American Heart Journal

VOL. 24 OCTOBER, 1942 NO. 4

Original Communications

CLINICAL STUDIES ON DIGOXIN, A PURIFIED DIGITALIS GLYCOSIDE

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THIS report deals with our observations on patients with congestive heart failure who were treated with digoxin, a pure crystalline glycoside. Although considerable work has been published on digoxin,[1] both experimental and clinical, there has been no study large enough to constitute a thorough clinical evaluation. It is not our purpose at this time to compare the various glycosides, or to indicate the relative superiority of any single preparation.

In recent years the availability of the purified digitalis glycosides has brought about renewed interest in digitalis therapy. Study of the glycosides has clearly demonstrated the inaccuracy of the bio-assay method, in that the cat unit potency of these preparations cannot be directly applied to man.[2] This makes it necessary to ascertain accurately the clinical potency of each of the glycosides in terms of actual weight. However, once this information is obtained, there is no variation in the potency of the sample, and, therefore, no need for repeated assays of different samples of the same preparation.

Digoxin was isolated from Digitalis lanata by Smith,[3] in 1930. It is a white crystalline substance which, on hydrolysis, yields one molecule of digoxigenin and three molecules of digitoxose. It is related to lanatoside C, but its molecule contains no glucose or acetyl grouping.

SELECTION OF PATIENTS

The study was conducted on hospitalized and ambulatory patients. The hospitalized patients were selected according to the criteria established in previous studies.[4] In all cases the criteria used in diagnosis were those of the New York Heart Association.[5] Patients with recent myocardial infarction, or other com-

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Received for publication Feb. 26, 1942.

plicating conditions, such as bronchopneumonia or glomerulonephritis, were excluded. Congestive heart failure was present to some degree during the period of hospitalization, although it may not have been discernible at the time of digitalization. All patients were cooperative. None were moribund or too ill to be followed adequately after digitalization. No patients were used who had received any digitalis preparation within at least three weeks prior to the beginning of the study.

METHOD

Before digitalization the maximum effect of the usual supportive measures was evaluated in each case. The patient was then digitalized with digoxin* according to one of three plans. Thirty-three patients were digitalized rapidly by a modification of the Eggleston method.[6] The initial dose varied between 0.75 and 2.0 mg. Thereafter, a dose ranging from 0.5 to 1.0 mg. was given every six hours until minor signs of toxicity were noted. The second plan consisted of administering single daily doses of 0.25 and 1.5 mg. to nine hospitalized and nine ambulatory patients. In both groups, on the hospitalized patients, observations were made daily in an effort to ascertain the minimal dose necessary to initiate a therapeutic effect and produce minor signs of toxicity. At least one electrocardiogram was taken shortly before digitalization, and others were made at frequent intervals, usually daily, thereafter. All patients were weighed daily to aid in evaluating changes in their cardiac status. This was particularly useful in gauging the therapeutic response of patients with normal sinus rhythm. The ambulatory patients were observed at one- or two-week intervals. Electrocardiograms in this group were taken when a significant therapeutic or toxic effect was observed clinically. All patients were observed closely for evidences of improvement, changes in ventricular and pulse rates, and symptoms and signs of toxicity.

In the third plan of study, each of 13 hospitalized patients, eight of whom had chronic auricular fibrillation with a rapid ventricular rate, received a single dose of digoxin intravenously. The dose varied between 1.5 and 2.5 mg. This relatively large dose was administered because our primary object was to study the rapidity of onset of effect. To insure this it was necessary to give a dose which was known to be well within the therapeutic range. No evidence of toxicity was noted when doses in this range were previously administered to seven normal subjects without heart disease. Herrmann[7] suggests similar doses in the treatment of patients with congestive heart failure. The intravenous preparation was administered so that 0.5 mg. of digoxin was diluted in 10 c.c. of physiologic saline solution. In this group the ventricular rates, pulse rates, arterial pressures, and venous pressures were taken until constant levels had been established. Digoxin was then administered, and the above observations were repeated at frequent intervals for several hours. Electrocardiograms were taken immediately before, and frequently during, the period of observation.

A study of the maintenance dose of digoxin was made in a group of 24 ambulatory patients, of whom 20 had chronic auricular fibrillation and four had normal sinus rhythm. These patients had no symptoms of diminished cardiac reserve or evidence of congestive heart failure when they were adequately maintained on a digitalis preparation. With the exception of those patients who received digoxin for initial digitalization, all patients were under observation for months or years prior to this study, so that their maintenance requirements of digitalis were known. For

*We are indebted to Burroughs Wellcome and Co., Inc., for the generous supply of material, and other aid in connection with this investigation. Digoxin was supplied in 0.25 and 1.0 mg. tablets. The latter were furnished for investigative use only, to facilitate administration of large doses. The parenteral preparation was supplied in ampoules of 0.50 mg. in alcoholic solution. Using the Hatcher-Brody technique for assay, 0.192 mg. of digoxin is equivalent to one cat unit.

maintenance studies, digoxin was administered in doses varying from 0.25 to 1.5 mg. daily. In those cases in which various doses were given, administration was continued for at least five weeks, and usually eight to ten weeks, in order to evaluate properly each daily dose. At each clinic visit the patients were observed for clinical evidence of congestive heart failure, variation in the ventricular rate, and signs of digitalis toxicity. Electrocardiograms were taken when the daily dose of the drug was changed or when toxicity was noted.

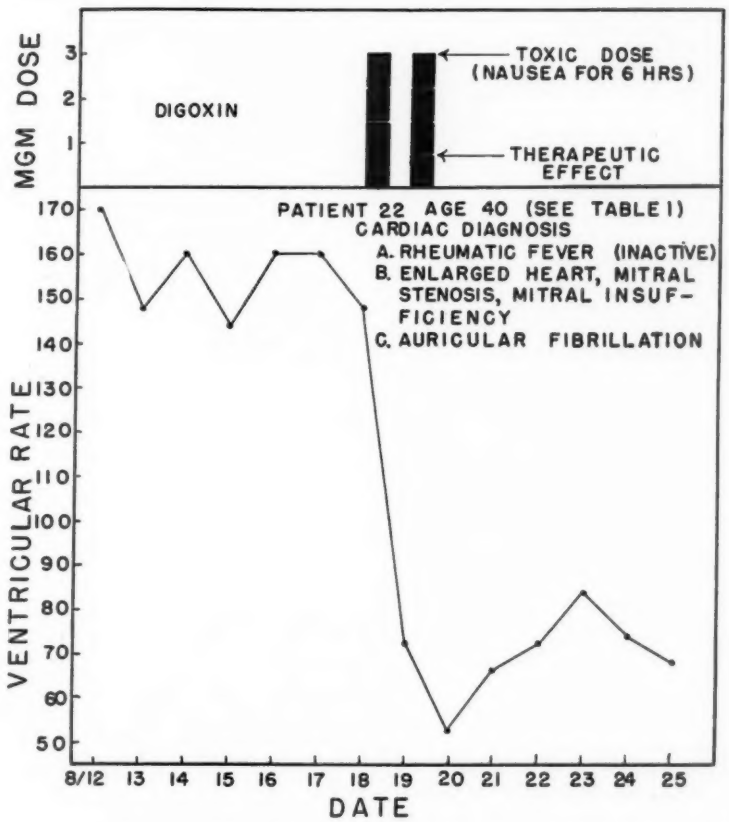

Fig. 1.—Rapid digitalization with digoxin orally in a patient with chronic auricular fibrillation. Therapeutic response noted within 24 hours after administration of 4.5 mg. Toxicity noted after 6.0 mg.

RESULTS

Digoxin was administered by a modification of the Eggleston method to 33 hospitalized patients, of whom 22 had normal sinus rhythm, seven had chronic auricular fibrillation, and four had auricular flutter. The essential data obtained in this group of patients are summarized in Table I. A satisfactory therapeutic response was observed in 23 cases, regardless of the nature of the underlying heart disease, rhythm, or degree of congestive heart failure (Fig. 1). With the exception of Patient 30, this response was noted within twenty-four or forty-eight hours with a dose ranging from 2.0 to 6.0 mg. (average, 3.75 mg.). In

TABLE

THERAPEUTIC AND TOXIC DOSES OF DIG

PATIENT	AGE	SEX	DIAGNOSIS			DEGREE OF CONGESTIVE HEART FAILURE*	WEIGHT IN POUNDS
			ETIOLOGIC	ANATOMIC	PHYSIOLOGIC†		
1	63	F	Arteriosclerosis	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	NSR	+	120
2	53	M	Arteriosclerosis and unknown	Enlarged heart. Aortic stenosis. Aortic insufficiency	NSR	±	166
3	58	M	Arteriosclerosis. Hypertension	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	NSR	+++	153
4	37	F	Rheumatic fever (inactive). Hypertension	Enlarged heart. Mitral stenosis. Mitral insufficiency	NSR	++	155
5	61	F	Arteriosclerosis. Hypertension	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	NSR	N	
6	76	F	Arteriosclerosis	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	NSR Left BBB	++	119
7	55	M	Arteriosclerosis. Pulmonary fibrosis	Enlarged heart. (Cor Pulmonale). Myocardial fibrosis. Coronary sclerosis	NSR	+	128
8	61	M	Arteriosclerosis. Hypertension	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	NSR	+++	116
9	64	M	Hypertension	Enlarged heart. Dilated aorta	NSR Incomplete left BBB	+	183
10	74	M	Arteriosclerosis	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	AF	+++	193
11	38	M	Rheumatic fever (inactive)	Enlarged heart. Mitral stenosis. Mitral insufficiency	AF	+++	193
12	57	M	Hypertension	Enlarged heart	NSR	±	133
13	51	F	Hypertension. Arteriosclerosis	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	NSR	++	109

*Ascertained by general appearance of patient and clinical response during a preliminary period of control.

†NSR, Normal sinus rhythm; BBB, bundle branch block; AF, auricular fibrillation; VPC, ventricular puncture contraction; VR, ventricular rate.

‡Excluding patient 30.

1

OXIN WITH RAPID DIGITALIZATION ORALLY

DOSE OF DIGOXIN IN MG.		THERAPEUTIC EFFECT	THERAPEUTIC DOSE IN MG.	TOXIC EFFECT	TOXIC DOSE IN MG	REMARKS
INITIAL DOSE	DOSE EVERY SIX HOURS					
1.0	0.5	Decreased dyspnea	3.0	Nausea and vomiting. Prolonged P-R interval (0.22 second)	5.0	
1.5	1.0			Nausea and vomiting. Prolonged P-R interval (0.23 second)	7.5	Therapeutic effect indefinite, minimal failure
1.5	1.0	Initiation of diuresis. Decreased dyspnea	4.5	Paroxysmal ventricular tachycardia (duration, 2 hours)	6.5	Toxicity was of brief duration and unaccompanied by nausea and vomiting
1.5	1.0	Decreased dyspnea and palpitation	3.5	Nausea	8.5	
2.0	N			Nausea and vomiting	2.0	Toxicity three hours after initial dose
1.0	1.0			Nausea	2.0	Patient digitalized two days after initial digitalization
1.5	1.0	Marked diuresis. Decreased dyspnea	2.5	Anorexia and nausea	4.5	
2.0	1.0	Diuresis. Decreased dyspnea	4.0	Anorexia and nausea	5.0	
2.0	1.0	Diuresis. Decreased dyspnea	3.0	Anorexia and nausea	6.0	
2.0	1.0	Diuresis	?	Nausea and vomiting	8.0	Therapeutic effect overshadowed by toxicity
2.0	1.0	Marked slowing of VR. Diuresis	3.0	Nausea	4.0	
2.0	1.0	Slowing of VR. Diuresis. Decreased dyspnea	4.0	Nausea	12.0	
2.0	1.0	Diuresis	6.0	Nausea and vomiting	6.0	Therapeutic effect overshadowed by toxicity
2.0	1.0			Nausea	3.0	Therapeutic effect overshadowed by toxicity

TABLE

PATIENT	AGE	SEX	DIAGNOSIS			DEGREE OF CONGESTIVE HEART FAILURE*	WEIGHT IN POUNDS
			ETIOLOGIC	ANATOMIC	PHYSIOLOGIC†		
14	60	F	Arteriosclerosis. Hypertension	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	NSR with VPC's	+	121
15	82	F	Arteriosclerosis	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	NSR with VPC's	N	122
16	37	M	Rheumatic fever (inactive)	Enlarged heart. Mitral stenosis. Mitral insufficiency	NSR	N	154
17	66	M	Arteriosclerosis	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	Auricular flutter	++	113
18	68	F	Arteriosclerosis	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	AF	+++	149+
19	52	M	Hypertension	Enlarged heart	AF	++	204
20	64	M	Arteriosclerosis	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	Auricular flutter	N	106
21	60	M	Arteriosclerosis. Hypertension	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	NSR	+	144
22	40	F	Rheumatic fever (inactive)	Enlarged heart. Mitral stenosis. Mitral insufficiency	AF	++	197
23	64	M	Arteriosclerosis. Hypertension	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	NSR	N	158
24	57	M	Arteriosclerosis. Syphilis	Enlarged heart. Dilated aorta. Aortic insufficiency	NSR	+	140
25	67	M	Arteriosclerosis. Hypertension	Enlarged heart. Myocardial fibrosis. Coronary sclerosis. Old myocardial infarct	NSR	+	115

I—CONT'D

DOSE OF DIGOXIN IN MG.		THERAPEUTIC EFFECT	THERAPEUTIC DOSE IN MG.	TOXIC EFFECT	TOXIC DOSE IN MG	REMARKS
INITIAL DOSE	DOSE EVERY SIX HOURS					
2.0	1.0	Diuresis	4.0	Anorexia and nausea	4.0	
2.0	1.0			Anorexia and nausea	4.0	
2.0	1.0			Anorexia, nausea, vomiting. Prolonged P-R interval (0.23 second)	8.0	
2.0	1.0	Change of auricular flutter to auricular fibrillation with control of VR. Diuresis	5.0	Nausea and vomiting	11.00	
2.0	1.0	Slowing of VR. Diuresis	2.0	Nausea	3.0	Condition too poor to be weighed previous to digitalization
2.0	1.0	Slowing of VR. Diuresis	5.0	Nausea and vomiting	11.0	
2.0	1.0	None		Nausea and vomiting	8.0	Increase in degree of A-V block, with no change in rhythm. Later received quinidine, with change to NSR
1.5	0.75	None		Nausea and vomiting	3.75	
1.5	0.75	Slowing of VR. Diuresis	4.5	Nausea and vomiting. Marked slowing of VR (52 per minute)	6.0	Slow VR persisted for 8 days after discontinuance of digoxin. Redigitalization with digitalis (whole leaf) produced similar therapeutic and toxic effects with 15 and 21 cat units, respectively
1.5	0.75			Nausea	12.00	
1.5	0.75	Diuresis	3.0	Nausea. Paroxysmal AF	5.25	
1.5	0.75	Diuresis	3.75	Nausea and vomiting	5.25	

TABLE

PATIENT	AGE	SEX	DIAGNOSIS			DEGREE OF CONGESTIVE HEART FAILURE*	WEIGHT IN POUNDS
			ETIOLOGIC	ANATOMIC	PHYSIOLOGIC†		
26	52	F	Arteriosclerosis. Hypertension	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	NSR	++	154
27	64	M	Arteriosclerosis	Enlarged heart. Myocardial fibrosis. Coronary sclerosis. Old myocardial infarct	NSR Left BBB	N	147
28	31	F	Hypertension	Enlarged heart	NSR	++	262
						++	265
29	77	F	Arteriosclerosis	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	AF	+	118
30	60	M	Arteriosclerosis	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	Auricular flutter. Left BBB	+	139
31	57	M	Arteriosclerosis. Hypertension	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	NSR	+	133
32	53	F	Hypertension	Enlarged heart	Auricular flutter	++	185
33	66	F	Arteriosclerosis. Hypertension	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	AF	++	99

I—CONT'D

DOSE OF DIGOXIN IN MG.		THERAPEUTIC EFFECT	THERAPEUTIC DOSE IN MG.	TOXIC EFFECT	TOXIC DOSE IN MG.	REMARKS
INITIAL DOSE	DOSE EVERY SIX HOURS					
1.5	0.75	Diuresis	3.0	Anorexia	3.75	
1.5	0.75			A-V nodal rhythm	6.0	
1.5	0.75	None		Nausea and vomiting	3.0	Patient redigitalized with digoxin five days later
1.5	0.75	Diuresis	3.0	Nausea and vomiting	4.5	
0.75	0.75	Slowing of VR	2.25	Nausea	3.75	Digitalized with digoxin intravenously four weeks previously (see Patient 9, Table IV)
2.0	1.0	Change in rhythm to auricular fibrillation	13.00	Marked slowing of VR	21.0	Digoxin was continued to a total dose of 42.75 mg. (171 cat units) without further evidence of toxicity
2.0	1.0	Disappearance of Cheyne-Stokes respiration and nocturnal dyspnea	6.0	Nausea and vomiting. A-V nodal rhythm and VPC's	8.0	
2.0	1.0	Change in rhythm to NSR	5.0	Nausea, vomiting and anorexia	9.0	
2.0	1.0	Slowing of VR. Diuresis	3.0	Nausea and vomiting	5.0	
Average‡			3.75		6.0	

TABLE

SLOW DIGITALIZATION WITH SINGLE DAILY

PATIENT	AGE	SEX	DIAGNOSIS			DEGREE OF CONGESTIVE HEART FAILURE*	WEIGHT IN POUNDS	DAILY DOSE OF DIGOXIN IN MG.
			ETIOLOGIC	ANATOMIC	PHYSIOLOGIC†			
1	45	M	Arteriosclerosis	Enlarged heart. Myocardial fibrosis. Coronary sclerosis. Old myocardial infaret	NSR	N	100	1.25
2	62	M	Arteriosclerosis. Hypertension and unknown	Enlarged heart. Myocardial fibrosis. Coronary sclerosis. Aortic insufficiency	NSR	N	139	1.50
3	67	M	Arteriosclerosis. Hypertension	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	NSR	N	260	1.50
4	66	M	Arteriosclerosis. Hypertension	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	AF	+	184	1.50
5	65	M	Arteriosclerosis	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	NSR	+	155	1.50
6	54	M	Arteriosclerosis	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	NSR Right BBB	N	135	1.50
7	65	F	Arteriosclerosis	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	NSR	+	126	1.25
8	54	F	Rheumatic fever (inactive)	Enlarged heart. Mitral stenosis. Mitral insufficiency	AF	+	108	1.00
9	59	F	Arteriosclerosis. Hypertension	Coronary sclerosis. Myocardial fibrosis. Old myocardial infaret	NSR	+	139	1.25

*Ascertained by general appearance of patient and clinical response during a preliminary period of control.

†NSR, Normal sinus rhythm; AF, auricular fibrillation; BBB, bundle branch block; VPC, ventricular premature contraction; VR, ventricular rate.

II

DOSES OF DIGOXIN IN HOSPITALIZED PATIENTS

THERAPEUTIC EFFECT	DAYS REQUIRED	THERAPEUTIC DOSE IN MG.	TOXIC EFFECTS	DAYS REQUIRED	TOXIC DOSE IN MG.	REMARKS
			Anorexia and nausea	3	3.75	
			Anorexia and nausea	6	9.0	
			Anorexia for evening meal	3	4.5	Same dose continued for total of 7 days without further toxicity
Slowing of VR	1	1.50	Anorexia and nausea. VPC's with coupling	5	7.5	
Diuresis	3	4.5	Anorexia for evening meal. Prolonged P-R interval (0.23 second)	5	7.5	
						Patient received 1.5 mg. for 18 days without clinical evidence of toxicity at time of discharge
			Anorexia and nausea. VPC's. Prolonged P-R interval. Runs of idioventricular rhythm	4	5.0	
Slowing of VR. Diuresis	3	3.0	Anorexia for evening meal	4	4.0	
Diuresis. Slowing of VR	4	3.75	Nausea and vomiting	3	3.75	

TABLE

SLOW DIGITALIZATION WITH SINGLE DAILY

PATIENT	AGE	SEX	DIAGNOSIS			DEGREE OF CONGESTIVE HEART FAILURE*	WEIGHT IN POUNDS	DAILY DOSE OF DIGOXIN IN MG.
			ETIOLOGIC	ANATOMIC	PHYSIOLOGIC			
1	38	M	Rheumatic fever (inactive)	Enlarged heart. Mitral stenosis. Mitral insufficiency	AF	+++	170	1.25
						+++	171	1.00
						+++	163	0.75
2	65	M	Arteriosclerosis. Hypertension	Enlarged heart. Myocardial fibrosis. Coronary sclerosis. Dilated aorta	AF	+++	157	1.50
						++	150	1.00
3	50	M	Rheumatic fever (inactive)	Enlarged heart. Mitral stenosis. Mitral insufficiency	AF	++	147	0.75
4	36	M	Rheumatic fever (inactive)	Enlarged heart. Mitral insufficiency. Aortic insufficiency	NSR	+	176	1.00
5	53	M	Unknown	Enlarged heart.	AF	+	167	1.50
6	25	M	Rheumatic fever (inactive)	Enlarged heart. Mitral stenosis. Mitral insufficiency. Aortic insufficiency	AF	+	150	1.00
7	61	M	Hypertension. Arteriosclerosis	Enlarged heart. Myocardial fibrosis. Coronary sclerosis. Old myocardial infarct. Dilated aorta	NSR	+	144	0.75
8	75	M	Arteriosclerosis	Enlarged heart. Myocardial fibrosis. Coronary sclerosis	AF	+	143	0.25
						+	145	0.50
9	50	M	Hypertension	Enlarged heart	NSR	+	193	1.00

*Ascertained by general appearance of patient and clinical response during a preliminary period of control.

III

DOSES OF DIGOXIN IN AMBULATORY PATIENTS

THERAPEUTIC EFFECT	WEEKS REQUIRED	TOXIC EFFECTS	WEEKS REQUIRED	REMARKS
Slowing of VR. Complete alleviation of failure. Diuresis	2			Patient discontinued medication after two weeks. Returned to clinic with heart failure six weeks later
Slowing of VR. Complete alleviation of failure. Diuresis	3			Patient continued this dose for total of 9 weeks without evidence of toxicity. Returned to clinic with heart failure 4 weeks later
None				Patient hospitalized after 1 week with persisting marked failure when he was redigitalized (see Table IV, Patient 1)
Slowing of VR. Diuresis. Complete alleviation of failure	1	VPC's with coupling	5	Medication was discontinued. Patient had moderate failure when he returned to clinic 7 weeks later
Exactly as above	1			Patient has continued this dose for over 7 weeks with no toxicity
Slowing of VR. Complete alleviation of failure	2			Patient has continued this dose for over 12 weeks without toxicity
Slow decrease in failure	6			Drug continued for 9 weeks without toxicity
Slowing of VR. Diuresis	3			Drug continued for 12 weeks without toxicity. (Patient had previously required large doses of digitalis preparations for maintenance)
Slowing of VR. Complete alleviation of failure	1	Nausea	7	
Diuresis	1	Nausea	3	
None				This dose continued for 12 weeks, then increased
Slowing of VR	3			Patient continued this dose for 9 weeks without toxicity
		Anorexia. Nausea. Vomiting		Unable to evaluate therapeutic response

TABLE

RESULTS OF DIGITALIZATION WITH

PATIENT	AGE	SEX	DIAGNOSIS			DEGREE OF CONGESTIVE HEART FAILURE*	WEIGHT IN POUNDS	DOSE OF DIGOXIN IN MG.
			ETIOLOGIC	ANATOMIC	PHYSIOLOGIC			
1	39	M	Rheumatic fever (inactive)	Enlarged heart. Mitral insufficiency. Mitral stenosis	AF	+++	175	1.5
2	64	M	Arteriosclerosis. Hypertension	Enlarged heart. Coronary sclerosis. Myocardial fibrosis	AF	+++	269	1.75
3	56	M	Arteriosclerosis. Hypertension. Pulmonary fibrosis and emphysema	Enlarged heart. Coronary sclerosis. Myocardial fibrosis	NSR	+++	168	2.5
4	50	F	Hypertension	Enlarged heart	NSR	++++	150	1.5
5	58	M	Arteriosclerosis. Hypertension	Enlarged heart. Coronary sclerosis. Myocardial fibrosis	AF	+++	188	2.5
6	71	F	Arteriosclerosis	Enlarged heart. Coronary sclerosis. Myocardial fibrosis	AF	+++	129+	1.5
7	54	M	Hypertension. Arteriosclerosis	Enlarged heart. Coronary sclerosis. Myocardial fibrosis	NSR VPC's	+++	156½	2.0

*Ascertained by general appearance of patient and clinical response during a preliminary period of control.

IV

SINGLE INTRAVENOUS DOSES OF DIGOXIN

INITIAL THERAPEUTIC EFFECT	TIME OF ONSET	FULL THERAPEUTIC EFFECT	TIME OF ONSET	TOXIC EFFECT	TIME OF ONSET	REMARKS
Slowing of VR (126-96)	15 min.	Diuresis. Fall in venous pressure	24 hr.	None		
Slowing of VR (128-96)	13 min.			None		Ventricular rate remained slowed, and lowered venous pressure persisted, although no other therapeutic effect was noted for eight days. Thereafter patient improved progressively, with complete alleviation of failure on bed rest without further cardiac medication
None		None		None		Patient showed no objective or subjective improvement after administration of the drug, possibly because of pulmonary disease
Fall in venous pressure (185-142 mm. H_2O). Slight subjective improvement. Diuresis	14 min.	Fall in venous pressure to 118 mm. H_2O. Continued subjective improvement	2½ hr.	None		
Fall in VR (95-74). Fall in venous pressure (205-177 mm. H_2O)	10 min.	Fall in venous pressure to 38 mm. H_2O. Marked clinical improvement. Diuresis	21 hr.	None		
None		None		VPC's with coupling. Runs of ventricular tachycardia	17 min. 65 min.	Patient showed no improvement. Continued to have auricular fibrillation with runs of ventricular tachycardia. Became rapidly and progressively worse and died on third day after digitalization
Fall in venous pressure (118-88 mm. H_2O)	8 min.	Clinical improvement. Diuresis. Fall in venous pressure to 47 mm. H_2O. Weight loss of 7 pounds	24 hr.	None		

TABLE

PATIENT	AGE	SEX	DIAGNOSIS			DEGREE OF CONGESTIVE HEART FAILURE*	WEIGHT IN POUNDS	DOSE OF DIGOXIN IN MG.
			ETIOLOGIC	ANATOMIC	PHYSIOLOGIC			
8	48	F	Rheumatic fever (inactive)	Enlarged heart. Mitral stenosis. Mitral insufficiency	AF	+	142	1.5
9	77	F	Arteriosclerosis	Enlarged heart. Coronary sclerosis. Myocardial fibrosis	AF	+	118½	1.5
10	39	F	Rheumatic fever (inactive)	Enlarged heart. Mitral stenosis. Mitral insufficiency. Dilated aorta	AF	+++	145	2.0
11	51	F	Arteriosclerosis	Enlarged heart. Mitral insufficiency. Coronary sclerosis. Myocardial fibrosis	AF	++	177	2.0
12	22	F	Rheumatic fever (inactive)	Enlarged heart. Mitral stenosis. Mitral insufficiency	AF	+	102	2.0
13	65	M	Arteriosclerosis	Enlarged heart. Coronary sclerosis. Myocardial fibrosis	Auricular flutter	+++	222	2.0

seven cases the therapeutic effect was indefinite, either because of the minimal degree of congestive heart failure or because it was overshadowed by toxic manifestations. In two cases the therapeutic and toxic doses were apparently identical, perhaps because digitalization took place rapidly. Three patients were not benefited from initial digitalization. No appreciable effect was noted on the auricular flutter of Patient 20, who subsequently regained normal rhythm with the help of quinidine. Patient 28 did not respond to the first course of digoxin, but five days later redigitalization with digoxin resulted in a satisfactory response. The toxic dose, with the exception of Patient 30, ranged between 2.0 and 12.0 mg. (average, 6.0 mg.). Patient 30, who had auricular flutter, required 13 mg. before a therapeutic effect could be observed, and 21 mg. over a period of five days before toxic manifestations occurred.

IV—CONT'D

INITIAL THERAPEUTIC EFFECT	TIME OF ONSET	FULL THERAPEUTIC EFFECT	TIME OF ONSET	TOXIC EFFECT	TIME OF ONSET	REMARKS
Fall in VR (160-120)	15 min.	Fall in VR to 97	1 hr.	None		
	15 min.	Fall in venous pressure from 182-75 mm. H_2O	4 hr.			
Fall in VR (101-88)	15 min.	Fall in VR to 79. Abolition of pulse deficit. Complete symptomatic relief	½ hr.	None		
Fall in VR (119-105)	15 min.	Fall in VR to 82. Marked relief of all subjective signs. Abolition of dyspnea and orthopnea	2½ hr.	None		
Fall in venous pressure (330-246 mm. H_2O)	60 min.					
Fall in VR (144-109)	15 min.	Fall in VR to 79. Marked subjective improvement	2 hr.	Nausea. Vomiting	2¼ hr.	
Fall in VR (120-98)	27 min.	Fall in VR to 70. Marked subjective improvement. Spontaneous sleep	1¼ hr.	None		
Venous pressure fall (128-95 mm. H_2O)	11 min.					Patient improved clinically, with increase in degree of A-V block for 2 hours and 20 minutes, at which time he abruptly lost consciousness, respiration failed, cyanosis appeared, and death ensued within a few minutes

The type of toxicity was in no way different from that usually observed with the whole leaf of digitalis purpurea. Anorexia, nausea, and vomiting were commonly the earliest manifestations. In one instance (Patient 3), a run of paroxysmal ventricular tachycardia was the only sign of toxicity. This, however, subsided rapidly when digoxin was discontinued, and did not affect the ultimate course of the patient. A change in rhythm occurred also in Patients 24 and 31, who developed auricular fibrillation and A-V nodal rhythm, respectively. These also were of short duration and disappeared spontaneously when the medication was stopped. Prolongation of the P-R interval was observed in three instances.

In the group of nine hospitalized patients (Table II) who received single daily doses of digoxin, ranging between 1.0 and 1.5 mg., it was possible to ascertain the therapeutic dose in only four cases. The others

did not have congestive heart failure at the time of digitalization. In these four cases the therapeutic dose was within the range noted for the rapid method of digitalization, but occurred, as was to be expected, a few days later. The toxic dose ranged from 3.75 to 9.0 mg. (average, 5.9 mg.). Although the same type of toxicity occurred, it was of short duration, and not as severe as that which was observed in the rapidly digitalized patients.

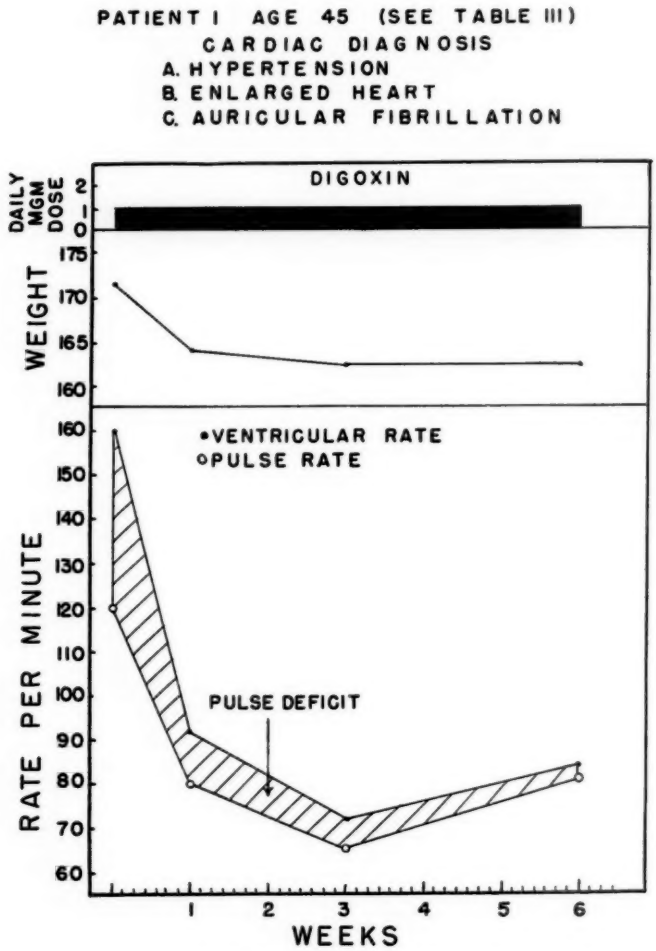

Fig. 2.—Slow digitalization achieved in an ambulatory patient with daily administration of 1.0 mg. of digoxin.

In eight of the nine ambulatory patients (Table III), slow digitalization was satisfactorily accomplished with a single daily dose of 0.50 and 1.5 mg. (Fig. 2). With the exception of Patient 4 of this group, improvement was noted within one to three weeks after the onset of therapy. It was possible to study digitalization by this method with two

trials in two cases and in three trials in another. Four patients developed toxicity. This occurred several weeks after initiating therapy, which was in contrast to the hospital group who received the same daily doses.

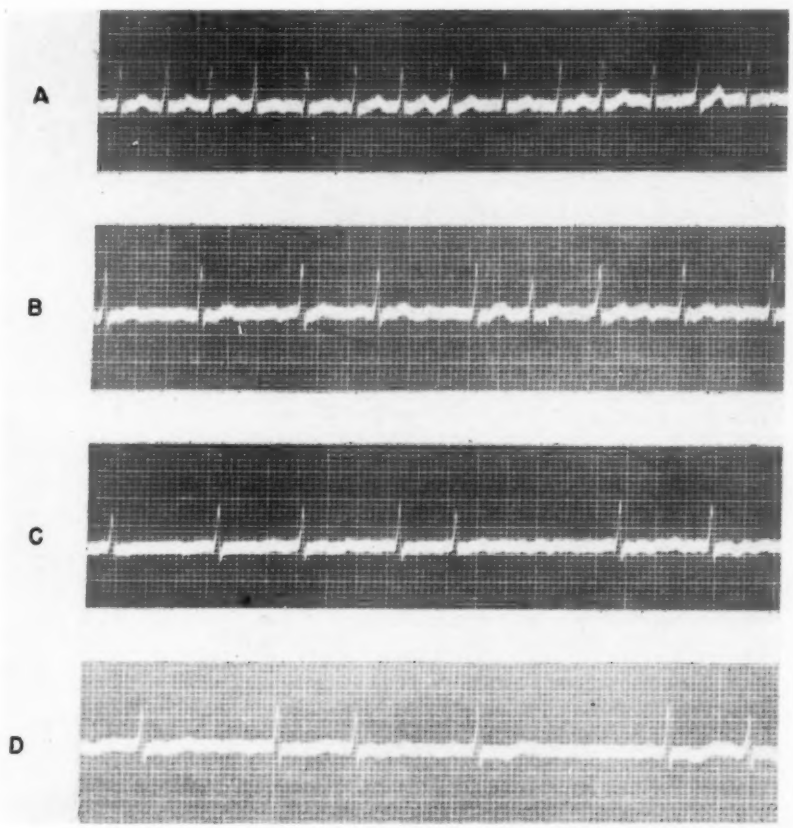

Fig. 3.—Electrocardiograms (Lead 2) of Patient 8, Table IV, with auricular fibrillation, after digitalization by means of a single intravenous dose of 1.5 mg. of digoxin. *A*, Control: ventricular rate, 170 per minute. *B*, Twenty minutes after digoxin: ventricular rate, 108 per minute. *C*, Forty-five minutes later: ventricular rate, 84 per minute. *D*, Four hours and forty-five minutes later: ventricular rate, 72 per minute.

Ten of the 13 patients who were digitalized with a single intravenous injection of digoxin (Table IV) showed objective evidence of improvement. In the group of patients with auricular fibrillation this was usually dramatic, with slowing of the ventricular rate within fifteen minutes after the drug's administration (Fig. 3). A concomitant fall in venous pressure and diuresis were also initiated, and were the best indices of effectiveness in patients with normal sinus rhythm. Patient 6, a 71-year-old woman with arteriosclerotic heart disease, developed ventricular premature systoles, with coupling, seventeen minutes after 1.5 mg. of digoxin, and subsequently developed ventricular tachycardia,

which persisted until death occurred forty-eight hours later. A second patient (Number 13), with auricular flutter, died suddenly two and one-half hours after digitalization with 2.0 mg. of digoxin intravenously. Ten of the 13 patients showed no evidence of toxicity.

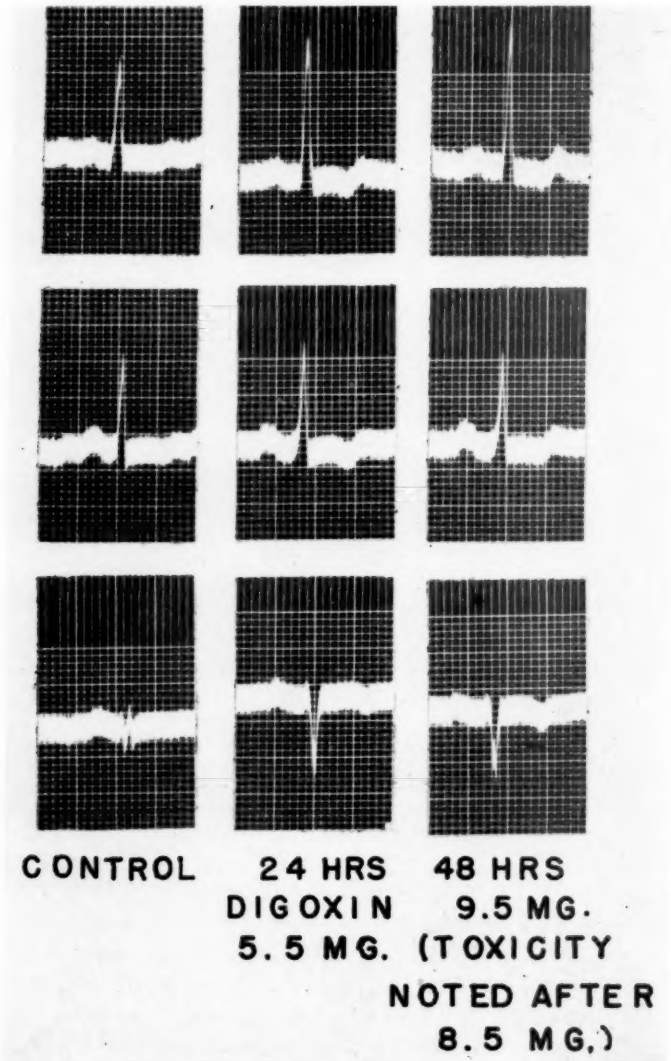

Fig. 4.—Alterations in electrocardiographic complexes produced by digitalization with digoxin orally.

Maintenance with digoxin in single daily doses was achieved in the majority of patients without difficulty. The dose varied between 0.25 and 1.5 mg.; 20 of the patients required 0.5 to 1.0 mg. In terms of cat unit potency, the patients required approximately twice as much digoxin as of digitalis leaf.

Electrocardiographic changes were noted in practically all cases, regardless of the method of digitalization. These consisted of the typical T and S-T segment depressions (Fig. 4). It was our impression that these changes were not usually as striking as those which are produced by digitalis leaf.

DISCUSSION

Digoxin was found to fulfill all of the requirements 4[b] which are demanded of a satisfactory digitalis preparation when it is given orally. The ventricular rate in patients with auricular fibrillation was controlled, and diuresis occurred in the majority of the rapidly digitalized patients within twenty-four hours. In order to compare the potency of powdered digitalis leaf with that of digoxin, it is necessary to translate the milligram dosage values of digoxin into cat units. Since 0.192 mg. of digoxin are equivalent to one cat unit, the clinical potency is the same as that of digitalis leaf. The average therapeutic and toxic doses, as ascertained by rapid digitalization, were 19.5 cat units (3.75 mg.) and 31 cat units (6.0 mg.), respectively. The ratio of toxic to therapeutic doses was also found to be similar to that of digitalis leaf. In the hospital group who were digitalized by giving large single daily doses, the toxic dose was found to be almost identical to that which was observed when the Eggleston method was used. The toxic dose was larger in the ambulatory group, who were digitalized similarly. This may have been due to the fact that observations in the ambulatory group were necessarily less frequent than in the hospital group. However, because these two groups were not large, adequate conclusions cannot be drawn.

In the ambulatory group a considerably larger dose was required for maintenance than would have been expected from the observations in the group who were rapidly digitalized by the Eggleston method; this was probably because of the rapid elimination of digoxin, which has been noticed by previous investigators.[1a, c, 8] Schwab[1c] stated that, because of rapid elimination, the establishment of a maintenance dosage of digoxin would be difficult. Herrmann[8] and Schwab both estimated that the amount required for maintenance was approximately one-third of the quantity necessary to produce full digitalization. These conclusions were not supported by our study. We had no difficulty in establishing a maintenance dosage, and this was usually found to be considerably less than one-third of that estimated for full digitalization. Twelve patients of the group of 24 required 0.5 mg. or less, and only three required more than 1.0 mg. for adequate maintenance.

In the course of our study, however, we did note other indications of rapid "dissipation" of digoxin. In the rapidly digitalized group toxicity was usually of brief duration; it commonly disappeared within a few hours after discontinuance of the drug. In several patients the toxicity which was produced by initial digitalization with digoxin subsided within twenty-four to forty-eight hours, even though an adequate

daily maintenance dose of digitalis leaf was immediately given at the onset of toxicity. (This was first noted when a maintenance dose was inadvertently started on a patient who had become toxic.) The same phenomenon was observed by Fahr and LaDue[9] with lanatoside C. In a number of patients who were digitalized with single daily doses, administered at noon, anorexia and nausea appeared only for several hours at night. These patients were able to continue taking the same daily dose for several additional days without further development of toxicity. Studies on the dissipation of digoxin are still in progress.

Digoxin was remarkably and rapidly effective when given parenterally. The therapeutic effect was evident within fifteen minutes in those patients who responded. It must be emphasized, however, that the same dangers which are inherent in the parenteral use of all digitalis preparations are present. It is never possible to predict accurately the proper individual therapeutic dose, and, therefore, when large doses are used, the possibility of causing severe toxicity and even death must be remembered. Two deaths in our series followed the administration of digoxin intravenously. One was a patient with auricular flutter whose death may well have been caused by embolism. The second was an elderly woman who had severe failure, and, therefore, rapid digitalization was thought advisable. Despite lack of clinical or electrocardiographic evidence, there is a very good possibility that her death may have been caused by concomitant myocardial infarction. Permission for autopsy was not obtained in either of these cases.

Our study indicates that the following are the proper doses of digoxin. For rapid digitalization with the oral preparation, an initial dose of 1.5 mg. should be given, followed by doses of 0.75 mg. at six-hour intervals until the desired therapeutic effect has been achieved. At this time a daily maintenance dose of 0.50 or 0.75 mg. can be given. This dose may be increased or decreased by 0.25 mg., according to the requirement of the individual patient. For digitalization with single daily doses we suggest giving 1.0 to 1.5 mg. Because our studies on the use of digoxin parenterally were done with the primary purpose of evaluating the time of onset of therapeutic response, and because we are still studying the effect of the administration of smaller amounts, we are not prepared at this time to recommend doses with this method of administration.

SUMMARY

1. The effects of digoxin, a purified crystalline glycoside which is obtained from digitalis lanata, were studied on 55 hospitalized and 33 ambulatory patients.

2. The average therapeutic and toxic doses with rapid administration orally were 3.75 and 6.0 mg., respectively.

3. The requirement for maintenance with digoxin was approximately twice that of digitalis leaf.

4. Evidences in favor of rapid dissipation of digoxin are discussed.

5. Digoxin by the parenteral route produces an effective response, usually within fifteen minutes. The inherent dangers of parenteral digitalization are considered.

6. Digoxin satisfies the established criteria for a reliable, potent digitalis preparation.

The authors acknowledge the assistance of Dr. Ludwig W. Eichna, of the Department of Medicine, New York University College of Medicine, and of several members of the resident staff of Lenox Hill Hospital, in obtaining data after the parenteral administration of digoxin.

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PERSISTENCE OF EFFECT AFTER DIGITALIZATION BY COMBINED USE OF DIGITALIS AND OUABAIN

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IN A previous communication[1] the combined use of ouabain and digitalis was shown to be a satisfactory method of producing digitalization. At that time it was thought that the slowing of the ventricular rate of patients with chronic auricular fibrillation brought about by giving the two drugs together would persist longer than when ouabain was given intravenously by the method of Wyckoff and Goldring,[2] but for a shorter time than when digitalis leaf was administered orally by the Eggleston[3] method. Since data in support of this assumption were not presented, it is the purpose of this study to compare the relative rates of dissipation of the effects of ouabain and digitalis leaf when administered alone and in combination. The relative efficacy of the three methods of digitalization will not be considered.

Since digitalis glycosides exhibit numerous and interrelated effects upon the cardiovascular system, it is possible that not all these effects persist for the same length of time in the same or different persons. The study was therefore limited to the main effects of digitalis on patients with congestive heart failure and chronic auricular fibrillation, i.e., slowing of the ventricular rate and improvement in myocardial efficiency, as manifested by relief from symptoms and signs of congestive heart failure.

SELECTION OF PATIENTS

The clinical data on the patients whom we studied are outlined in Table I. All had chronic auricular fibrillation, and, when not under the influence of digitalis, had subjective and objective evidence of congestive heart failure, and tachycardia with a ventricular rate of more than 100 per minute. These patients varied in the degree of their failure when under the influence of the drug. Some were asymptomatic with maintenance doses of digitalis. Others had moderate to severe congestive heart failure, and required diuretics, in addition to digitalis, for symptomatic relief. However, it was possible, even in such cases, to estimate the cardiac reserve, so that there was no difficulty in observing an increase in degree of failure when digitalis action had ceased. Nine of the twelve patients had inactive rheumatic heart disease and three had combined arteriosclerotic and hypertensive heart disease. Patients with myocardial infarction were excluded. All were in a chronic disease hospital where it was possible to observe them for a sufficient length of time before beginning the study, and where hospitalization could be continued long enough to complete the observations. Finally, all patients were cooperative and lent themselves well to the study.

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Received for publication Feb. 27, 1942.

TABLE I

CLINICAL DATA ON THE PATIENTS STUDIED

PATIENT	AGE	SEX	CARDIAC DIAGNOSIS		MAINTENANCE DOSE OF DIGITALIS (IN GRAMS)	SEVERITY OF HEART FAILURE*
			ETIOLOGIC	ANATOMIC		
1	39	F	Rheumatic fever	Enlarged heart Mitral stenosis Mitral insufficiency	0.1-0.2	Moderate —mild†
2	32	M	Rheumatic fever	Enlarged heart Mitral stenosis Mitral insufficiency	0.2-0.3	Severe
3	67	M	Arteriosclerosis Hypertension	Enlarged heart Coronary sclerosis Myocardial fibrosis	0.1	Mild
4	23	M	Rheumatic fever	Enlarged heart Mitral stenosis Mitral insufficiency Aortic insufficiency	0.1-0.2	Moderate
5	29	M	Rheumatic fever	Enlarged heart Mitral stenosis Mitral insufficiency	0.1	Mild
6	39	F	Rheumatic fever	Enlarged heart Mitral stenosis Mitral insufficiency Aortic insufficiency	0.2	Severe
7	36	F	Rheumatic fever	Enlarged heart Mitral stenosis Mitral insufficiency	0.2	Severe
8	54	F	Rheumatic fever Hypertension	Enlarged heart Mitral stenosis	0.1-0.2	Severe
9	57	F	Arteriosclerosis Hypertension	Enlarged heart Coronary sclerosis Myocardial fibrosis	0.1	Mild
10	38	F	Rheumatic fever	Enlarged heart Mitral stenosis Mitral insufficiency Aortic insufficiency	0.1	Moderate
11	80	F	Arteriosclerosis Hypertension	Enlarged heart Coronary sclerosis Myocardial fibrosis	0.05-0.1	Mild
12	15	F	Rheumatic fever	Enlarged heart Mitral stenosis Mitral insufficiency	0.1-0.2	Moderate

*The estimation of the degree of the congestive heart failure was based upon the severity of the symptoms and signs of failure which the patient presented when not under the influence of digitalis, and upon the degree to which these symptoms were relieved by digitalization or maintenance doses of digitalis.

†In this patient the symptoms were of moderate failure early in the study; later her symptoms became definitely milder.

METHOD

During a preliminary control period which ranged from one to several months, the effectiveness of a maintenance dose of digitalis leaf was observed in order to estimate the cardiac reserve, i.e., the degree of compensation which could be obtained with the drug, in conjunction with rest in bed and limitation of fluid intake. Digitalis was then discontinued, and the patients were observed daily for signs and symptoms of development of, or an increase of, congestive heart failure and tachycardia. When this state occurred and persisted in bed, the patients were

rapidly and fully digitalized by one of three methods. The procedure was then repeated, but digitalization was performed each time by a different method. However, regardless of the method used, no more digitalis or ouabain was given until all the effects of the previous digitalization had disappeared. In this way nine of the twelve patients were digitalized more than once by each method. Twenty-one digitalizations were done with ouabain alone, twenty with the combined drugs, and sixteen with digitalis leaf alone.

The method of Wyckoff and Goldring[2] was used for digitalization with ouabain alone. An initial dose of 0.5 mg. (5 cat units) of ouabain* was given intravenously, followed by successive doses of 0.1 mg. every half-hour or every hour until toxic signs appeared or the ventricular rate fell below 70 per minute. The combined use of ouabain and digitalis, as previously reported,[1] consisted of administering 0.5 mg. of ouabain intravenously simultaneously with 0.4 to 0.8 grams (4 to 8 cat units) of digitalis leaf* orally. The third method was that recommended by Eggleston,[3] and consisted of giving, initially, one-half of the total estimated dose, and the remainder in divided doses every six hours. Since we had had previous experience with the ouabain and digitalis leaf preparations which were used, it was relatively easy to ascertain the amount of each drug each patient would require to obtain the full effect. Since, cat unit for cat unit, ouabain is twice as potent in man as digitalis leaf, the appropriate dose of either preparation was known after the first digitalization with either drug alone.

Before each digitalization an effort was made to allow the original degree of congestive heart failure and tachycardia to return. Also, we attempted to maintain a constant level of digitalization by administering the drugs in doses sufficient to produce, for each comparison, a similar degree of toxicity. In this manner any question of insufficient or inconsistent dosage was obviated as far as possible.

All of the patients were given the same general diet, and the salt and fluid intake was kept as constant as possible. The majority of the patients were kept continually in bed; several were semiambulatory when they did not have failure. However, in each case, a constant degree of activity was maintained. Each patient was examined daily for evidences of congestive heart failure, and carefully questioned as to subjective symptoms, such as dyspnea, orthopnea, palpitation, and pain in the liver area. The ventricular and radial pulse rates, counted for one minute, were recorded daily, or more frequently when indicated. The patients were weighed daily, and blood pressures were recorded at frequent intervals. Electrocardiograms were taken several times during the control period, twenty-four hours after each digitalization, and every third or fourth day thereafter.

During the course of the study, it soon became apparent that factors other than the digitalis preparation or method of digitalization influenced the persistence of the digitalis effect in a given case. For example, any alteration in the degree of the congestive heart failure, produced either by mercurial diuretics or by mechanical means, such as paracentesis, would greatly influence the ventricular rate. For this reason, while we were comparing the effects of the three methods, those factors which might alter the cardiovascular status of the patient were avoided or excluded from the study. However, in two instances (patients 1 and 8) such a change in status occurred, but because the change was between the series of comparisons and did not occur while comparing the methods with one another, the results are included.

*Ampules of ouabain, in a concentration of 2.5 cat units per cubic centimeter, and tablets of digitalis (whole leaf), of multiple cat unit strength, were supplied by Carroll Dunham Smith Pharmacal Company, Orange, New Jersey. The potency of these preparations was confirmed in our laboratory by the Hatcher and Brody method of assay.

RESULTS

The details of the individual digitalizations are summarized in Table II. The results are considered in three categories, namely, the time, in days, required for the reappearance of congestive heart failure, the development of tachycardia (ventricular rate 100 or over), and a precipitous rise of the ventricular rate to a level usually associated with uncontrolled auricular fibrillation. On the average, these reappeared earliest after digitalization with ouabain alone, next with combined ouabain and digitalis, and last with digitalis alone. The means and their standard errors for each method of digitalization are presented in Table III.

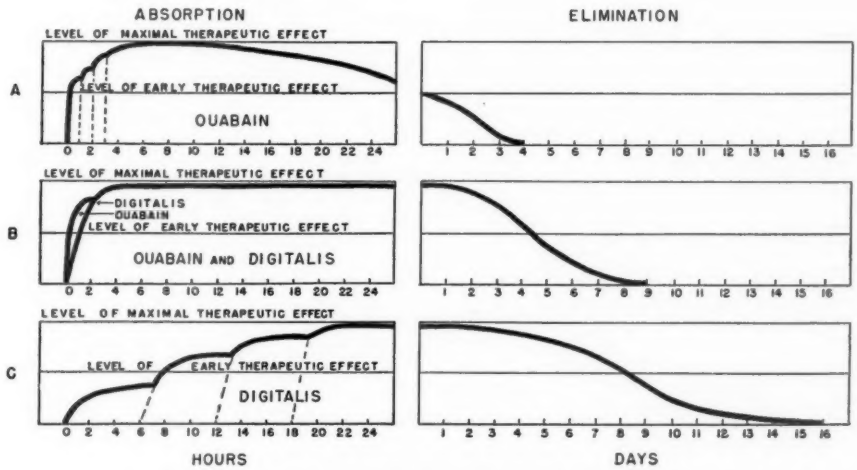

Fig. 1.—Schematic representation of absorption and elimination: *A*, of ouabain given intravenously by the method of Wyckoff and Goldring; *B*, digitalis and ouabain in combination by the method of Batterman, Rose, and DeGraff; and *C*, digitalis leaf given orally by the method of Eggleston. (By elimination is meant the persistence of digitalis effect upon the ventricular rate of patients with auricular fibrillation.)

Calculation of Fisher's t-function indicates that the differences between the three sets of means are highly significant, and cannot be ascribed to sampling errors. It should be noted that these data are based upon fifty-seven digitalizations of twelve patients. This group is too small to show that there is less variation among trials carried out upon the same patient than there is for the whole group. Other factors than the drugs used or method of digitalization may influence the persistence of the effect. For instance, it is probable that in a few instances a sudden alteration in the cardiovascular status occurred which was beyond our control. The patient's cardiac reserve, or its clinical counterpart, the degree of congestive heart failure, also constituted a source of variation.

To complete the schematic presentation of data on absorption and elimination with each method, as shown in the previous communication,[1] Fig. 1 is included.

TABLE II

SUMMARY OF RESULTS ON PERSISTENCE OF DIGITALIZATION WITH THE THREE METHODS DESCRIBED IN TEXT

PATIENT	TRIAL	METHOD OF DIGITALIZATION	DOSE IN CAT UNITS*	STATUS AT TIME OF DIGITALIZATION		EVIDENCE OF FULL DIGITALIZATION		TIME IN DAYS FOR REAPPEARANCE OR INCREASE IN CONGESTIVE HEART FAILURE	VENTRICULAR RATE AT ONSET OF CONGESTIVE HEART FAILURE	TIME IN DAYS FOR VENTRICULAR RATE TO EXCEED 100 PER MINUTE	TIME IN DAYS FOR APPEARANCE OF PRECIPITOUS RISE IN VENTRICULAR RATE	REMARKS
				WEIGHT IN POUNDS	VENTRICULAR RATE	CLINICAL	VENTRICULAR RATE					
1	1	Ouabain	6	117½	148	Nausea Vomiting	58	3	88	4	5	Two days after first signs of failure apical rate rose to 132
	2	Ouabain and digitalis	9	118½	146	Nausea Vomiting	66	4	90-94	5	5	One day after first signs of failure apical rate rose to 126
	3	Digitalis	12	118	142	Anorexia Nausea	60	6	96	7	7	
	4	Ouabain	6	108¼	132	Anorexia Nausea	67	9	106	9	10	Between the third and fourth trials patient spontaneously lost all edema with a weight loss of ten pounds
	5	Ouabain and digitalis	9	110	138	Nausea Vomiting	66	10	106	10	13	
	6	Digitalis	12	112½	136	Anorexia Nausea	70	19	128	19	19	Failure and sudden tachycardia occurred simultaneously
	7	Ouabain and digitalis	9	111	134	Nausea	68	15	112	15	17	
2	1	Ouabain	7	126½	120	Nausea Headache	70	3	110	3	4	Failure noted with apical rate of 110. Precipitous rise occurred following day
	2	Ouabain and digitalis	11	125½	128	Anorexia Nausea	70	5	120	5	5	Failure and sudden tachycardia occurred simultaneously

*In the combined method of digitalization, 0.5 mg. (equivalent to 5 cat units) of ouabain was used in every instance except in case 12, in which 0.3 mg. was administered. This patient was 15 years of age and weighed only 72 pounds.

†This patient expired suddenly seven hours after the administration of 0.7 mg. (divided doses) of ouabain intravenously. Autopsy revealed typical healed rheumatic lesions of aortic and mitral valves and an anomaly of the left coronary artery, but no immediate cause of death was found.

2	3	Digitalis	14	125	130	Nausea	75	8	112	8	11	Sudden tachycardia occurred three days after signs of failure, and rate of 100 per minute appeared
	4	Ouabain	7	124½	130	Nausea Headache Dizziness	68	14	108	4	5	
	5	Ouabain and digitalis	11	125½	135	Nausea Vomiting	68	6	142	6	6	Failure and sudden tachycardia appeared simultaneously
3	1	Ouabain	7	165½	120	Nausea Anorexia	66	3	92	4	5	
	2	Ouabain and digitalis	11	165	121	Anorexia	63	12	116	10	12	Although rate exceeded 100 on the tenth day, it fell again only to rise suddenly on the twelfth day, accompanied by failure
	3	Digitalis	14	171	122	Nausea Anorexia Extrasystoles	70	27	110	27	29	
4†	1	Ouabain	7	118¼	136	Anorexia Nausea	66	3	112	3	4	
	2	Ouabain and digitalis	11	120	140	Nausea Vomiting	66	6	108	6	11	For five days rate ranged between 106 and 120 before suddenly rising to 146
	3	Digitalis	14	120	136	Nausea Vomiting	60	14	142	9	14	Unable to detect any sign of failure while rate ranged between 104 and 114. Rise to 142 was sudden
4	4	Ouabain and digitalis	11	118	146	Nausea	74	10	143	8	10	Unable to detect failure before rate rose suddenly to 143
	5	Digitalis	14	117¾	140	Nausea Anorexia	68	15	122	12	15	Unable to detect failure with rate from 96 to 112

TABLE II—CONT'D

PATIENT	TRIAL	METHOD OF DIGITALIZATION	DOSE IN CAT UNITS*	STATUS AT TIME OF DIGITALIZATION		EVIDENCE OF FULL DIGITALIZATION		TIME IN DAYS FOR REAPPEARANCE OR INCREASE IN CONGESTIVE HEART FAILURE	VENTRICULAR RATE AT ONSET OF CONGESTIVE HEART FAILURE	TIME IN DAYS FOR VENTRICULAR RATE TO EXCEED 100 PER MINUTE	TIME IN DAYS FOR APPEARANCE OF PRECIPITIOUS RISE IN VENTRICULAR RATE	REMARKS
				WEIGHT IN POUNDS	VENTRICULAR RATE	CLINICAL	VENTRICULAR RATE					
5	1	Ouabain	7	135	118	Anorexia Nausea	69	5	108	5	8	
	2	Ouabain and digitalis	11	134½	116	Anorexia Nausea Extrasystoles	62	14	114	12	14	Rate exceeded 100 on twelfth day only to fall and rise suddenly accompanied by failure on 14th day
	3	Digitalis	14	134½	116	Nausea	70	28	98	29	29	Precipitous rise one day after failure appeared
	4	Ouabain	7	136½	126	Anorexia Nausea	60	4	108	4	7	
6	1	Ouabain	6	141¾	118	Nausea Vomiting	68	3	86	4	4	Rate suddenly rose to 118 the day after failure was detected
	2	Ouabain and digitalis	9	147¼	128	Nausea Vomiting	51	6	124	6	6	Rate rose suddenly overnight from 82 to 124
	3	Digitalis	12	145	132	Anorexia	62	11	112	11	11	
	4	Ouabain	6	141¾	118	Nausea Vomiting	60	4	108	4	4	Rate rose suddenly overnight from 70 to 108
	5	Ouabain and digitalis	9	145¾	124	Nausea Vomiting	62	5	132	5	5	
	6	Digitalis	12	145¾	119	Anorexia Nausea	60	11	86	12	12	Definite signs of failure noted with rate of 86
7	1	Ouabain	7	128	120	Nausea Vomiting Coupling	48	3	87	3	3	Failure noted in morning with rate of 87. In afternoon rate rose suddenly to 112
	2	Ouabain and digitalis	9	123¾	154	Nausea Anorexia	60	4	80	6	6	Patient had slight temperature elevation at this time
	3	Ouabain	7	122	144	Nausea Vomiting	48	4	90	5	5	

8	1	Ouabain	7	120¼	126	Nausea Vomiting Extrasystoles	75	3	96-108	3	3	
	2	Ouabain and digitalis	11	120	134	Nausea Vomiting Extrasystoles	68	3	106	3	3	Rate rose overnight from 70 to 106, with a three pound weight gain
	3	Digitalis	14	118¼	122	Nausea Headache Vomiting Coupling	70	8	110	8	8	Following digitalization done after abdominal paracentesis
	4	Ouabain	7	111	126	Anorexia Nausea	66	5	108	5	5	Sudden rise from 86 to 108 without previous evidence of increased failure
	5	Ouabain and digitalis	11	106¾	138	Nausea Vomiting Extrasystoles	72	9	108	7	10	For two days rate ranged between 100 and 106 before failure was noted
	6	Digitalis	14	111¼	120	Nausea Vomiting Extrasystoles	60	14	118	14	14	
9	1	Ouabain	7	156	138	Anorexia Nausea	67	7	126	4	4	Rate over 100 for three days before failure was noted
	2	Ouabain and digitalis	11	150	148	Nausea Vomiting	70	37	130	34	36	Rate over 100 for three days before failure was noted
	3	Digitalis	14	151	122	Nausea Vomiting	76	37	120	37	37	Sudden overnight rise from 94
	4	Ouabain	7	150	132	Anorexia Nausea	68	7	126	3	7	
	5	Ouabain and digitalis	11	150	132	Nausea	69	24	120	22	22	Sudden rise in rate on twenty-second day from 70 to 110 without noting failure
10	1	Ouabain	6	121½	114	Anorexia Nausea	66	11	124	11	11	Sudden rise overnight, with failure
	2	Ouabain and digitalis	9	125	120	Nausea Vomiting Extrasystoles	52	12	80	12	12	Failure noted in morning with rate of 80. In afternoon rate rose suddenly to 116
	3	Digitalis	12	120	116	Nausea Anorexia	41	28	114	28	28	Sudden rise from 82 to 114 overnight

TABLE II—CONT'D

PATIENT	TRIAL	METHOD OF DIGITALIZATION	DOSE IN CAT UNITS*	STATUS AT TIME OF DIGITALIZATION		EVIDENCE OF FULL DIGITALIZATION		TIME IN DAYS FOR REAPPEARANCE OR INCREASE IN CONGESTIVE HEART FAILURE	VENTRICULAR RATE AT ONSET OF CONGESTIVE HEART FAILURE	TIME IN DAYS FOR VENTRICULAR RATE TO EXCEED 100 PER MINUTE	TIME IN DAYS FOR APPEARANCE OF PRECIPITIOUS RISE IN VENTRICULAR RATE	REMARKS
				WEIGHT IN POUNDS	VENTRICULAR RATE	CLINICAL	VENTRICULAR RATE					
11	1	Ouabain	7	111¼	128	Anorexia Nausea Extrasystoles	86	7	120	2	2	For five days rate above 100 but below 120 without signs of failure
	2	Ouabain and digitalis	11	111	122	Anorexia Nausea Extrasystoles	82	15	126	6	6	For nine days rate above 100 but below 126 without signs of failure
11	3	Digitalis	14	110½	132	Anorexia Nausea	66	27	122	13	?	For fourteen days rate above 100, but below 122 without signs of failure
	4	Ouabain	7	113	126	Nausea Vomiting	76	6	120	2	2	For four days rate over 100, but below 120 without signs of failure
12	1	Ouabain	5	72½	134	Nausea Vomiting	72	5	164	4	5	No failure with rate of 108. Sudden rise overnight to 164
	2	Ouabain and digitalis	7	70½	164	Nausea Vomiting	76	6	118	6	7	
	3	Digitalis	10	73	146	Nausea Vomiting	68	11	112	11	12	
	4	Ouabain	5	73½	148	Nausea Vomiting	65	4	138	4	4	
	5	Ouabain and digitalis	7	72½	138	Nausea Vomiting	64	8	112	8	8	On afternoon of eighth day rate suddenly rose to 144
	6	Digitalis	10	72	144	Nausea Vomiting	64	12	114	12	12	On afternoon of twelfth day rate suddenly rose to 138

TABLE III

ORIGINAL DEGREE OF CONGESTIVE HEART FAILURE	MEAN TIME IN DAYS REAPPEARANCE OF HEART FAILURE			MEAN TIME IN DAYS REAPPEARANCE OF TACHYCARDIA			MEAN TIME IN DAYS FOR REAPPEARANCE OF PRECIPITOUS RISE IN VENTRICULAR RATE		
	OUABAIN	OUABAIN AND DIGITALIS	DIGITALIS	OUABAIN	OUABAIN AND DIGITALIS	DIGITALIS	OUABAIN	OUABAIN AND DIGITALIS	DIGITALIS
Mild	6	18	28	4	15	25	6	17	28
Moderate	5	8	14	5	7	13	6	9	15
Severe	4	5	10	4	5	11	4	6	11
All degrees of failure ± standard error	4.9 ± 0.5	10.5 ± 1.8	17.2 ± 2.3	4.3 ± 0.5	9.6 ± 1.6	16.1 ± 2.3	5.1 ± 0.5	10.7 ± 1.7	17.2 ± 2.3
Total number of digitalizations by each method	21	20	16	21	20	16	21	20	16

The twelve patients are grouped with regard to degree of congestive heart failure, and the mean time is given in days for the persistence of digitalis effect by the three methods of digitalization. At the bottom of the table is given the mean time for all original degrees of failure with their standard errors and the number of digitalizations on which the results are based.

The patients with severe failure exhibited a shorter duration of digitalis action by any method of digitalization than did those with milder symptoms of diminished cardiac reserve (Table III). This is well illustrated by patients 1 and 8 (Table II), who had altered their cardiac status during the study. When patient 1 had severe failure, signs and symptoms reappeared in three, four, and six days after digitalization with each method, respectively, and nine, ten, and nineteen days, respectively, when compensation occurred spontaneously.

Whether other factors, such as age, sex, or type of heart disease, were significant in determining the persistence of the digitalis effect could not be concluded from this study.

Since an investigation of this sort affords an ideal opportunity for an analysis of the course of events from the time of full digitalization to the period of congestive heart failure, it is of interest to consider the frequency with which symptoms and signs of heart failure precede the recurrence of tachycardia and the precipitous rise in ventricular rate (Table IV). In 21 per cent of the trials, failure preceded the rapid ventricular rate, and in 50 per cent of the trials, failure appeared before the precipitous increase in rate.

TABLE IV

THE APPEARANCE OR INCREASE OF CONGESTIVE HEART FAILURE	NUMBER OF INSTANCES	PER CENT OF DIGITALIZATIONS
Before tachycardia (rate over 100) occurred	12	21
Simultaneously with tachycardia	31	55
After tachycardia occurred	14	24
Before precipitous rise in ventricular rate occurred	27	48
Simultaneously with precipitous rise	23	41
After precipitous rise occurred	6	11

The percentage of all digitalizations in which symptoms and signs of heart failure precede, occur simultaneously with, or follow, the recurrence of tachycardia and the precipitous rise in ventricular rate.

COMMENT

It should be made clear that this study was limited to patients with chronic auricular fibrillation who, when not under the influence of digitalis, showed signs and symptoms of congestive heart failure and tachycardia. Whether or not similar results would be obtained with other forms of heart disease which have different characteristics must await further investigation.

As might be expected on theoretical grounds, the duration of the effect of ouabain and digitalis in combination was intermediate between that of oubain alone and that of digitalis alone. Thus, ouabain maintained a slow ventricular rate for a mean period of 4.3 days, ouabain and digitalis, for 9.6 days, and digitalis leaf, for 16.1 days. It should be emphasized that what is being measured in this study is not actual elimination of the drugs, but persistence of their effect.

Cognizance of this difference was stressed by Gold,[4] and is the basis for explaining in part the variations noted in the same or different persons. It is well known that, after initial digitalization with ouabain, a patient can tolerate, within 24 hours, a subsequent dose of ouabain or digitalis leaf as if no ouabain had been given previously. This would indicate rapid elimination of the drug, and yet the initial digitalization will last, on the average, for four days. Although the elimination of digitalis leaf is much slower, as demonstrated by Pardee[5] and Gold,[4] it is conceivable that here also the effect will outlast the actual elimination of the drug.

Abundant evidence, both clinical and laboratory, has accumulated to attest the fundamental actions of digitalis—an increase in the force of systolic contraction[6] and an increase of the mechanical efficiency of the heart muscle.[7] This brings about restoration to normal function and improvement in the cardiac reserve and compensation within the limits of the severity of the heart disease. Previous studies on the persistence of this action of digitalis are lacking chiefly because undue emphasis has been placed on the ventricular rate. Considering, therefore, the reappearance of congestive heart failure, the action of ouabain will persist on the average for 4.9 days, that of ouabain and digitalis combined for 10.5 days, and that of digitalis leaf for 17.2 days.

That great variation in the persistence of the digitalis effect occurs not only in different persons but also in the same person at different times is clear from the earlier studies,[2, 8] and also from our investigation. The patients who had the most severe heart failure, who required, in general, a larger dose of digitalis for maintenance, and who usually showed some signs of decompensation when they were fully digitalized exhibited a shorter duration of effect than did those with milder symptoms of failure and a better cardiac reserve. This is probably one of the important reasons why differences in persistence of effect are observed in different patients, even though they are digitalized to the same degree and by the same method. However, other factors certainly are present. Although the work of Boas[9] was not directly concerned with the persistence of digitalis effects, the factor of disturbed "vagus accelerator balance," which occurs in fever and hyperthyroidism, probably is another reason for variations in duration of effect.

The relationship of the recurrence of heart failure to tachycardia is of particular interest in view of the present concept[10] that the slowing of the ventricular rate is primarily due to improvement of the circulation and secondarily to depression of the conducting system. Thus, slowing of the ventricular rate has been attributed to reflex stimulation of the vagus when compensation is restored. It is to be expected, therefore, that when the process is reversed, tachycardia should occur in the effort to maintain an adequate circulation. At first glance our results might not appear to support this interpretation, for,

on the average, tachycardia and congestive heart failure seemed to recur at the same time. However, on closer analysis, when the course of events are grouped together, regardless of previous method of digitalization, in only 24 per cent of the cases did tachycardia occur before failure reappeared. In an almost identical number of instances, 21 per cent, failure preceded the tachycardia, whereas, in 55 per cent, it seemed to occur simultaneously. Furthermore, when one considers a very rapid ventricular rate usually found in uncontrolled auricular fibrillation, failure preceded this state in almost half of the instances, and in only 11 per cent of the digitalizations was this reversed. However, when each patient is considered individually, there is no adequate means of ascertaining what the optimum ventricular rate for compensation should be. The appearance of failure with a rate of less than 100 per minute might signify that this rate was a "tachycardia" for this patient, and therefore detrimental to myocardial efficiency. Nevertheless, it is our belief that the dissipation of the effects of digitalization occurs in the following order. First, there is a gradual increase in the ventricular rate as the myocardial and vagal components of the digitalis action progressively decrease. The heart then responds at a rate compatible with the demands of the underlying cardiac reserve. As the myocardial effects of digitalis diminish, or because the increased ventricular rate places an added burden upon the heart, the patient develops signs and symptoms of congestive heart failure. This initiates a reflex mechanism which causes a further rise in the ventricular rate in an effort to maintain the circulation. Such an explanation would account for the "tachycardia" which occurs in many instances before the onset of failure, whereas an "uncontrolled" rapid ventricular rate in the majority of instances occurs "simultaneously" or after the development of failure.

SUMMARY

1. Digitalization with ouabain, digitalis alone, and with the two in combination was carried out twenty-one, sixteen, and twenty times, respectively, in twelve patients with chronic auricular fibrillation.

2. The persistence of the effect upon the ventricular rate and control of the congestive heart failure were shortest after digitalization with ouabain alone, longer with ouabain and digitalis combined, and longest with digitalis alone.

3. The digitalis action was shortest by any method of digitalization in the patients who had severe congestive heart failure.

4. The relationship between the rapid ventricular rate of auricular fibrillation and congestive heart failure is discussed.

The authors wish to express their appreciation to Dr. J. Murray Steele, Director of Third Medical Division, Welfare Hospital, for his valuable suggestions and criticisms; and to Dr. Robert A. Lehman for the statistical analysis of the results.

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AN ELECTROCARDIOGRAPHIC AND CLINICAL STUDY OF LANATOSIDE C

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RECENT clinical studies[1] have demonstrated the rapidity with which lanatoside C acts in the presence of congestive heart failure. These studies, however, do not include graphic or definite substantiating physical evidence.

It was the purpose of this investigation to compare, electrocardiographically, the effect on the myocardium of lanatoside C intravenously with that of digitalis purpurea by mouth. Many are of the opinion that the action of orally administered digitalis purpurea is for the most part sufficiently rapid, as compared with that of a glucoside given intravenously. It has been shown repeatedly that intravenous therapy is desirable for patients who are suffering from gastrointestinal disturbances, or are in extremis, when the absorption of a drug such as digitalis is definitely slowed. In the latter instance the time element may be an important factor in therapy. Recent observations by Fahr and LaDue and others[2-6] have demonstrated that the rapid clinical effectiveness and low toxicity of lanatoside C are due to its chemical composition. In view of these observations it was felt that electrocardiographic study of patients who were receiving this drug might offer additional confirmation of a digitalis effect.

Lanatoside C is one of the three crystalline, stable, initial glycosides of digitalis lanata. It has no counterpart in digitalis purpurea, and occurs only in the lanata plant. The exact relationship between digitalis purpurea and digitalis lanata has been elucidated by the extensive studies of Stoll.[7] He has shown that the hitherto best known glycosides of digitalis purpurea, digitoxin and gitoxin, are products of degradation which have lost one acetyl and one glucose molecule. Digitalis glycosides consist of aglycones, chemically bound to a varying number of sugars. Smith[8] has shown that the aglycone of lanatoside C differs from the other aglycones (genins) of digitalis purpurea and lanata. Although the aglycones possess the cardioactive properties, the sugar components appear to influence absorbability and fixation power. Therefore, it was felt that electrocardiographic observations should be made, for it is known that different preparations of digitalis vary somewhat. Rothlin,[9] Chen and co-workers,[10] and others have shown experimentally that the

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Lanatoside C is marketed by Sandoz Chemical Works, Inc., under the name of Cedilanid.

Received for publication Feb. 13, 1942.

pharmacologic effectiveness of these glycosides is enhanced by increasing the sugar content. Visscher and Peters[11] measured the energy metabolism of the heart and showed that lanatoside C increases the mechanical efficiency of the failing heart more rapidly and with a greater margin of safety than other preparations.

The cat unit assay (Hatcher Brody method) was ignored in this investigation, because recent studies by Gold and his associates[12] have clearly shown that cat units are no indication of the therapeutic potency of digitalis in man. Moreover, since lanatoside C is a pure crystalline substance, biologic assay is not necessary.

LaDue[13, 14] has shown that lanatoside C can be given in therapeutic doses to human beings over a long period of time without danger of producing morphologic changes in the myocardium. This has been confirmed experimentally by the fact that, when complete digitalizing doses were given intravenously to dogs every day for thirty days, the heart muscle was found to be histologically normal. This observation led to the bold method of administration used in this study, namely, the one-unit dosage.

MATERIAL AND METHODS OF STUDY

The criteria of a digitalis effect were the time necessary to obtain maximal depression of the RS-T segment in Lead II of the electrocardiogram, the rapidity with which the signs and symptoms of congestive failure disappeared, and the time required for the abolition of the segment changes. The standard digitalis purpurea leaf (U.S.P.) was used in one group because it is routinely used in our wards at the General Hospital.

Normal Controls.—Each of two normal, healthy adults received 1.6 mg. (8 c.c.) of lanatoside C intravenously over a period of sixty seconds, and two others were given 16 grains of digitalis purpurea leaf orally on a fasting stomach in a single dose. Four-lead electrocardiograms were recorded prior to the administration, and at intervals of fifteen minutes thereafter for a period of two hours. Further tracings were taken at varying intervals for as long as seventy-two hours.

Congestive Failure.—Forty patients with congestive failure were divided into two groups, irrespective of age, etiology, or severity of the congestive failure. The patients in one group received 16 grains of digitalis purpurea orally, and those in the other group received a single dose of 1.6 mg. of lanatoside C intravenously. Electrocardiograms were recorded in a like manner, and the response was observed clinically.

Particular attention was given to the incidence of toxic effects. Because of the severity of the congestive failure in some cases it was sometimes impossible to continue this study over a prolonged period of time. In such cases, or when complications required other methods of therapy, these were instituted.

RESULTS

In the two normal controls who received lanatoside C, the maximal depression of the RS-T segment occurred in thirty minutes in one, and in twenty-five minutes in the other (Table I and Fig. 1). A digitalis effect, however, was first noted in the electrocardiogram approximately fifteen minutes after the injection of lanatoside C, as manifested by a slight depression of the RS-T segment. Throughout the entire period

TABLE I

COMPARATIVE EFFECTS OF LANATOSIDE C (1.6 MG. I.V.) AND WHOLE LEAF OF DIGITALIS PURPUREA (1.2 GM. ORALLY) ON RS-T SEGMENT AND HEART RATE

MAXIMUM RS-T SEGMENT CHANGE

Patients Receiving Lanatoside C (1.6 mg. I.V.)

Control Normals

A. 30 min. } Aver. maximum RS-T
B. 25 min. } change = 27.5 min.

Patients With Congestive Failure

NO.	HOURS	
1	1½	Average time for maximum RS-T change 3 hours 6½ minutes. Without Case No. 3, 2 hours 45 minutes
2	5½	
3*	8	
4	2½	
5	2	
6†	3½	
7	2	
8	3½	
9	2½	
10‡	4	
11	3	
12	3	
13	1½	
14	4	
15	4	
16	2½	
17	4	
18	1½	
19	2½	
20	2	

Patients Receiving Digitalis Purpurea (1.2 Gm. orally)

Control Normals

C. 6½ hours } Average 6 hr.
D. 6 hours } 15 min.

Patients With Congestive Failure

NO.	TIME	
1	13 hr.	Average time for maximum RS-T change = 14 hours 24 minutes
2	13 hr. 20 min.	
3	12 hr. 30 min.	
4	14 hr. 30 min.	
5	13 hr.	
6	14 hr. 30 min.	
7	14 hr. 45 min.	
8	15 hr.	
9	14 hr. 40 min.	
10	15 hr.	
11	16 hr.	
12	14 hr. 20 min.	
13	13 hr. 40 min.	
14	14 hr.	
15	14 hr. 40 min.	
16	15 hr. 20 min.	
17	15 hr. 30 min.	
18	15 hr. 10 min.	
19	15 hr. 30 min.	
20	14 hr. 40 min.	

MAXIMUM SLOWING EFFECT ON HEART RATE

Patients Receiving Lanatoside C (1.6 mg. I.V.)

Control Normals

A. 20 minutes from 86 to 80 } Average
B. 15 minutes from 78 to 66 } 17½ min.

Maximum pulse reduction determined at one-hour intervals during 24 hours.

NO.	TIME		FROM	TO
1	3 hr. 40 min.		180§R	80
2	2 hr. 30 min.		108	62
3	4 hr.		140	78
4	4 hr.		156	74
5	5 hr.		100§	72
6	2 hr.		130§R	105
7	2 hr. 10 min.		116	140
8	3 hr.		150§	86
9	3 hr.		110	80
10	4 hr.	Average	150§R	84
11	3 hr. 30 min.	3 hr.	120§	70
12	2 hr. 30 min.	15 min.	114§	90
13	3 hr. 30 min.		150	88
14	3 hr. 15 min.		86§	82
15	5 hr. 30 min.		108§	62
16	5 hr.		120	70
17	4 hr. 10 min.		116	90
18	– 30 min.		120	110
19	2 hr. 30 min.		96	80
20	2 hr.		100	88
		Average	123.5	80.4

Patients Receiving Digitalis Purpurea (1.2 Gm.)

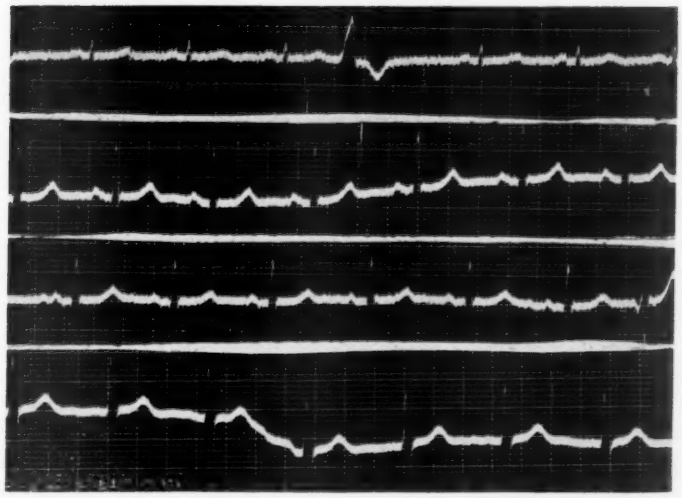
Effect Heart Rate

A. 6 hours from 90 to 82
B. 6 hours from 78 to 78

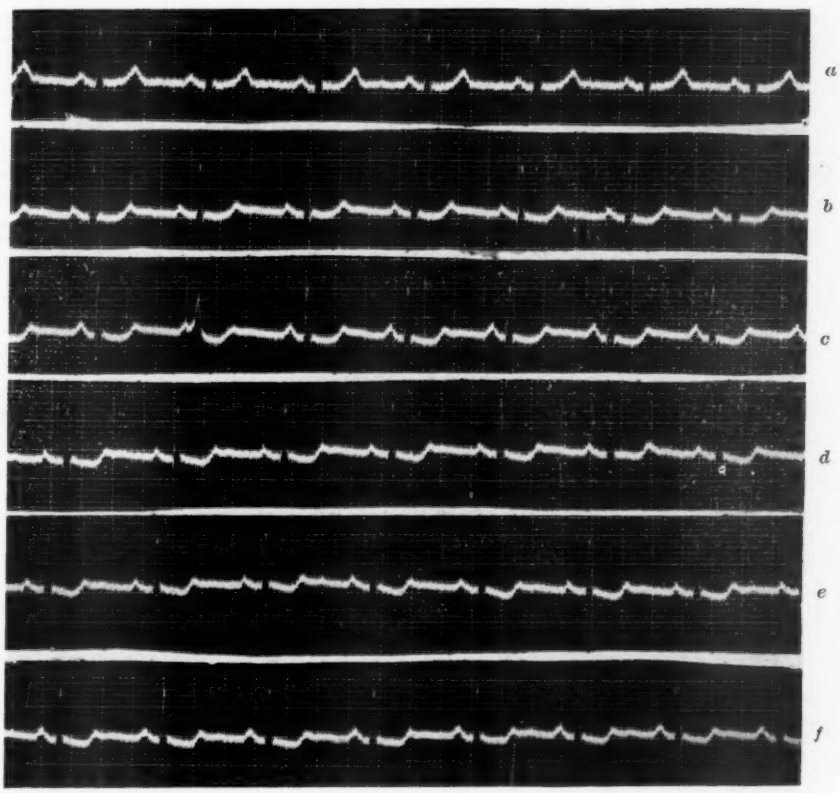
Maximum pulse reduction determined at one-hour intervals during 24 hours.

NO.	TIME		FROM	TO
1	12 hr.		156	74
2	8 hr. 20 min.		110	90
3	16 hr.		96	80
4	16 hr. 10 min.		132§	78
5	9 hr.		90	80
6	15 hr.		88	70
7	12 hr.		110§	102
8	12 hr.		96	88
9	8 hr. 30 min.		86	86
10	16 hr.	Average	120	108
11	9 hr. 40 min.	11 hr.	110§	74
12	12 hr. 15 min.	27 min.	120§	70
13	8 hr.		88	84
14	12 hr.		90	82
15	9 hr.		110	96
16	12 hr.		96	96
17	9 hr. 20 min.		108	92
18	12 hr. 40 min.		146§	110
19	7 hr.		112§	80
20	8 hr. 30 min.		110	76
		Average	108.7	85.8

*First record obtained eight hours after administration.
†Died pneumonia.
‡Died myocardial infarction.
§Patients with auricular fibrillation. R, normal sinus rhythm re-established.



A.



B.

Fig. 1.—Effect of lanatoside C, intravenously, on normal myocardium. *A*, Standard electrocardiographic leads on normal prior to administration of lanatoside C—1.6 mg. intravenously. *B*, Serial tracings taken in Lead 2. *a*, At time of injection of 8 c.c. of lanatoside C; *b*, fifteen minutes later; *c*, thirty minutes later; *d*, one hour twenty minutes later; *e*, one hour thirty minutes later; *f*, two hours later, digitalis effect receding.

of observation there was no evidence of digitalis toxicity in these controls. The two normal persons who received digitalis purpurea leaf orally on a fasting stomach showed a maximal digitalis effect upon the RS-T segment in six hours and thirty minutes and six hours, respectively. Both suffered from extreme nausea which persisted for twelve to fourteen hours after medication. A digitalis effect upon the electrocardiogram of these two patients was first noted approximately four hours after the administration of the drug. It was noted that the RS-T segment returned approximately to normal within sixteen hours in the two patients who received lanatoside C, whereas in those who received the whole leaf orally, a segment change was in evidence for as long as forty-eight hours.

Fig. 24.—J. L. A. Auricular fibrillation with rapid ventricular rate, ventricular premature beats, and left axis deviation.

Congestive Failure.—Of the twenty patients with congestive failure who received lanatoside C, two died during the study, one of lobar pneumonia, the other of myocardial infarction. Because of a psychosis in one case, it was impossible to repeat the tracings until eight hours after the administration of the drug. In this group the average time required for the maximal change in the RS-T segment was three hours and six and a half minutes. If the psychotic patient is excluded, the average time required for the maximal change in the RS-T segment was two hours and forty-five minutes. Only one of this group suffered from nausea. As was the case in Fahr's series, within three

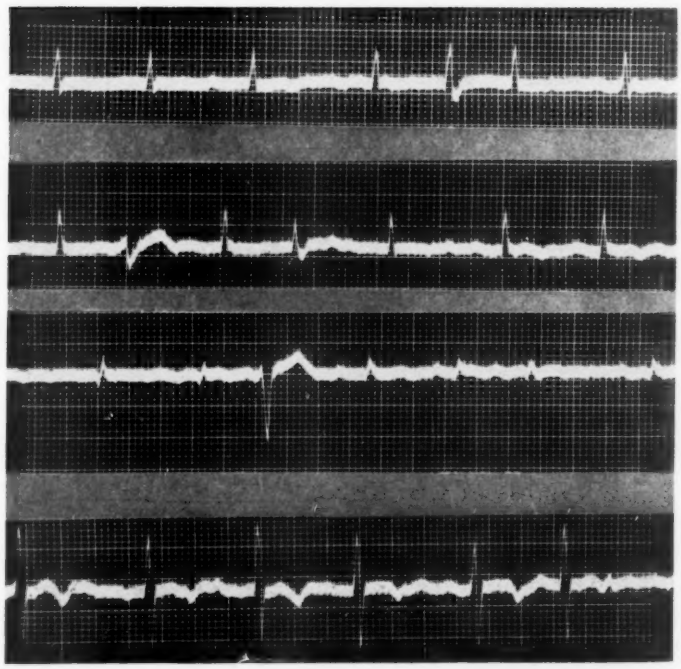


Fig. 2*B*.—J. L. A. Recorded twenty minutes after the intravenous administration of 1.6 mg. of lanatoside C. Definite digitalis effect, with appreciable slowing of the rate.

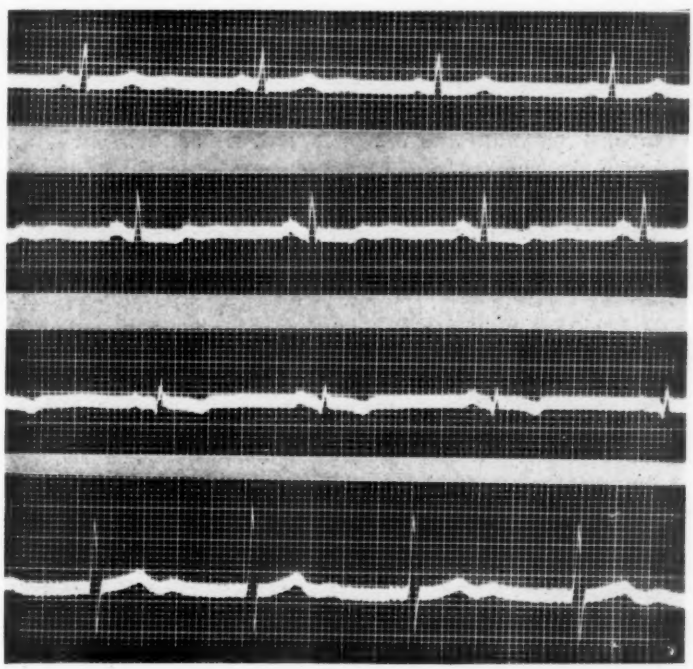


Fig. 2*C*.—J. L. A. Three hours after the administration of 1.6 mg. of lanatoside C. Normal sinus rhythm re-established, with definite slowing of the heart rate.

hours the average heart rate was reduced from 121 beats per minute to approximately 85. It was felt that at least part of this reduction in rate may have been a sinus effect. Inasmuch as frequent observations were made on the heart and pulse rate over this period, it is very unlikely that errors occurred. Of the surviving eighteen patients, all presented definite clinical evidence of improvement within a period of six hours. Nine patients of this group had auricular fibrillation. Of these, three recovered normal sinus rhythm within a period of twenty-four hours. Only one patient had a first degree block (A-V conduction time, 0.24 second) shortly after lanatoside C was given. Delay in A-V conduction appeared to be the exception rather than the rule in this series. One patient had slight nausea after the administration of lanatoside C. This nausea continued for a period of forty-eight hours.

In those with congestive failure who received digitalis purpurea orally, the average time required for a maximal change in the RS-T segment was approximately fourteen hours and twenty-four minutes. A digitalis effect on the RS-T segment was first noted eight and one-half hours after the drug was given. Eight of this group suffered from severe nausea and vomiting which were traceable specifically to the drug. There was an average reduction in the heart rate of approximately 30 beats per minute in the entire group within twenty-four hours after the administration of the whole leaf. Not unlike the group which received lanatoside C, a gradual clinical improvement was noted twenty-four hours later. The auricular fibrillation which was present in six cases in this group continued throughout the entire period of observation. The excretion of urine was increased equally in both groups. Because all of the patients in these groups continued to take digitalis after the study was discontinued, no return of the segments to normal was observed.

One patient who received lanatoside C presented an unusual clinical course which we were able to follow electrocardiographically, both prior to and after the administration of the drug. Because of the unusual circumstances, a brief summary of this case is given.

CASE REPORT

J. L. A., a white man 78 years of age, was admitted to the hospital on Jan. 28, 1941, complaining of vomiting, hiccough, insomnia, epigastric pain, and generalized weakness of seventy-two hours' duration. His past history was negative except for a surgical operation on his gall bladder four years prior to admission. At this time many stones were removed. Physical examination revealed a lean, elderly man, with no physical abnormalities other than epigastric tenderness. A tentative diagnosis of acute pancreatitis was made. Laboratory examination revealed a mild secondary anemia (hemoglobin, 70 per cent Sahli; erythrocyte count, 3,800,000; and polymorphonuclear leucocytes, 16,000). The urine was negative. On Feb. 9, 1941, while drinking a glass of milk, he was suddenly seized with a severe pain in the upper part of his abdomen. The temperature rose to 104° F., and extreme rigidity and tenderness were noted in the epigastrium;

roentgenologic examination revealed gas in the upper part of the abdomen, suggesting mild ileus. Soon after the appearance of these symptoms the patient's pulse rate became very rapid and irregular. Dyspnea made its appearance within a few hours, and was soon accompanied by moderate edema of the lungs and lower extremities. An electrocardiogram (Fig. 2*A*) disclosed auricular fibrillation with a rapid ventricular rate. While the temperature was still in the vicinity of 104° F., 1.6 mg. of lanatoside C were given intravenously because of the rapidly developing congestive failure; this was at 6 P.M. on February 17. Twenty minutes later there was a noticeable reduction in the pulse rate and heart rate (Fig. 2*B*), and at 9 P.M. the pulse rate was 70 and sinus rhythm had returned (Fig. 2*C*). At this time the electrocardiogram showed full digitalization. Laparotomy was performed at 10 P.M., and a diagnosis of peritonitis was made. Sinus rhythm continued throughout the entire operation. The patient had a stormy postoperative course, but his congestive failure continued to improve, and there was no reappearance of the auricular fibrillation.

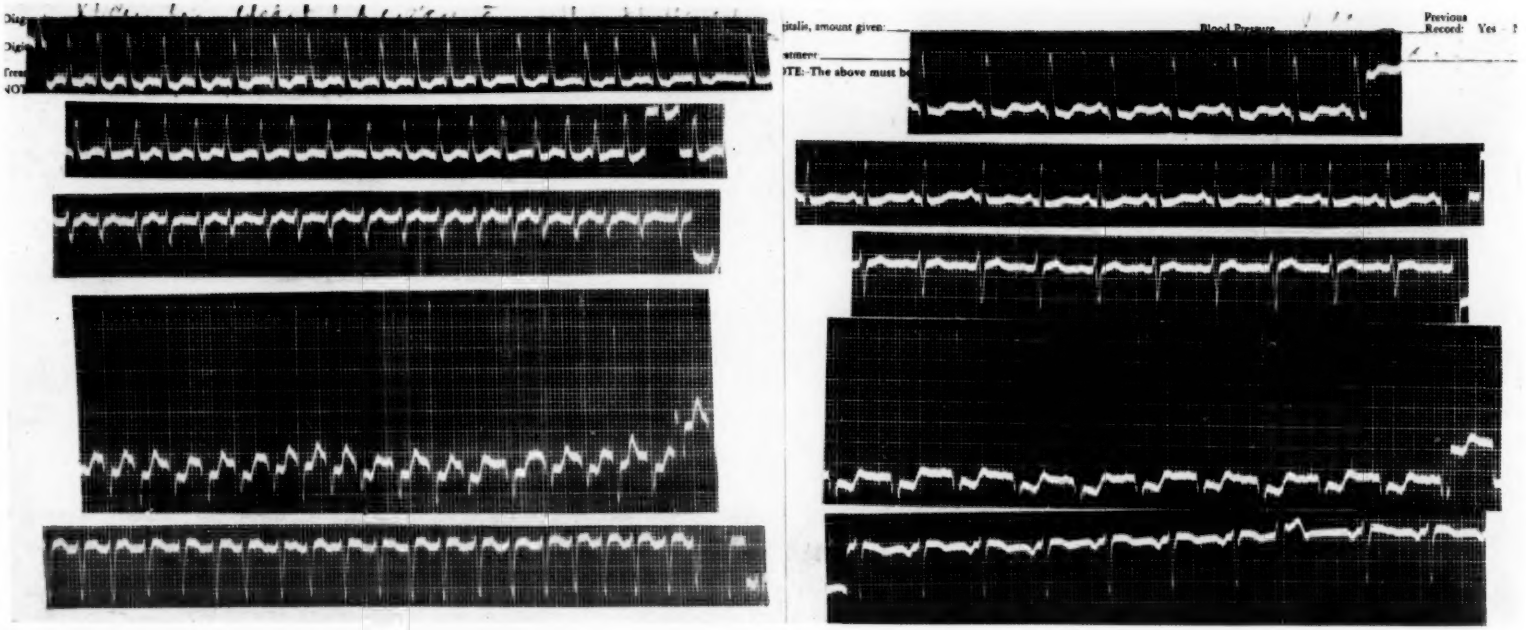
This case is reported because the desired therapeutic effect of digitalis was obtained during the course of acute congestive failure complicating a septic surgical condition. The presence of sepsis in no way inhibited the action of lanatoside C. Granting that the auricular fibrillation was paroxysmal and would possibly have terminated spontaneously, one is certainly led to believe that the drug proved its effectiveness.

DISCUSSION

The results obtained in this study from the intravenous administration of lanatoside C have shown that this drug exerts its maximal effect on the RS-T segment eleven to twelve hours sooner than a comparable dose of digitalis purpurea. If this criterion is acceptable, it should be of value in the treatment of congestive failure, especially since the segment changes are accompanied by clinical improvement in a like period of time. Although the material presented here is not large, and the results need further confirmation, encouraging evidence was obtained relative to the rapid action and low toxicity of this glucoside.

It is suggested that lanatoside C be given intravenously when the element of time is an important consideration in the treatment of congestive failure. This drug may also prove valuable for patients who are suffering from nausea and gastrointestinal disturbances when rapid digitalization is indicated. It is interesting that in the entire group of patients who received lanatoside C, the only side effect which could be attributed to its administration was nausea, and this was noted in only one case. On the other hand, nausea and vomiting occurred frequently after the oral administration of the digitalis leaf. Eight of the twenty patients with congestive failure suffered from these symptoms. Both of the control subjects, with no evidence of cardiac disease, developed severe nausea which was definitely traced to digitalis leaf. This observation leads one to believe that lanatoside C is comparatively free from the objectionable properties of the whole leaf.

It should be noted that of the eleven patients with auricular fibrillation, three regained normal sinus rhythm after the administration of



A. *B.*

Fig. 3.—*A*, Auricular fibrillation with rheumatic heart disease. Ventricular rate about 200 per minute. Quinidine failed to alter rhythm. *B*, 1.6 mg. of lanatoside C given intravenously at 10 A.M. Electrocardiogram taken at 10:30 A.M. Rhythm now normal. Left axis deviation. Possible changes in RS-T segment caused by digitalis.

lanatoside C (Fig. 3). The fact that this drug may aid in the re-establishment of normal sinus rhythm has been previously noted by many observers. Not a single patient with auricular fibrillation in the group in which digitalis purpurea was given by mouth regained normal rhythm throughout the entire period of observation.

With respect to maintenance of the digitalis effect, this study offers some interesting data. In the controls who received lanatoside C, the digitalis effect on the RS-T segment disappeared entirely within a period of sixteen hours, whereas this effect persisted for a period of forty-eight hours or more in the controls who received digitalis purpurea by mouth. It is clear that in order to retain the digitalis effect for a prolonged period of time, lanatoside C must be given intravenously at fairly frequent intervals, and it is therefore preferable to employ a digitalis preparation which contains all the glycosides for continued maintenance therapy. For those patients who do not require rapid digitalization or are not suffering from gastrointestinal disturbances, the preparations of digitalis now in common use are satisfactory.

SUMMARY AND CONCLUSIONS

1. The average time required for the development of maximal RS-T segment changes in the controls of this study after the administration of 1.6 mg. of lanatoside C intravenously was 27.5 minutes, as compared to six hours and fifteen minutes after giving 16 grains of digitalis purpurea by mouth.

2. In the presence of congestive failure, the intravenous administration of lanatoside C produced the maximal alteration of the RS-T segment within two to three hours, which was eleven to twelve hours sooner than when digitalis purpurea was given orally.

3. It seemed that the clinical manifestations of congestive failure disappeared with greater rapidity in the group of patients who received lanatoside C.

4. In the four controls the RS-T segment returned to normal in approximately sixteen hours after the administration of a single dose of 1.6 mg. of lanatoside C, and in approximately forty-eight hours after the administration of 16 grains of digitalis purpurea orally in a single dose.

5. These observations suggest that lanatoside C should be employed intravenously when rapid action is important in the treatment of congestive failure, or when gastrointestinal absorption of digitalis cannot be relied upon.

6. Unlike digitalis purpurea, lanatoside C does not produce untoward effects because it is more rapidly eliminated and seems to lack the nausea-producing elements of the whole leaf.

7. Our observations indicate that lanatoside C will prove to be a valuable drug in the treatment of congestive failure, especially when quick action is desired or when gastrointestinal symptoms are troublesome.

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UROLOGIC HYPERTENSION AS AN ENTITY

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THE studies to be reported in this paper were undertaken because of the occasionally striking cases we have observed[1] in which hypertension was found in the presence, not of Bright's disease, but of extrarenal disorders of the urinary tract. Since it is obviously fallacious to argue merely from occasional coincidences, we prepared, in 1939, a review[2] of the records of 600 private patients with persistent elevation of blood pressure. After taking out of this series the 26 cases (4.34 per cent) in which the hypertension could be accounted for by parenchymal renal disease (glomerulonephritis, Bright's disease, and other intrarenal or "medical" forms of kidney disease), we found a residue of 101 cases (16.8 per cent) in which the hypertension was concomitant with various types of urologic disease (various extrarenal or "surgical" forms of disease of the urinary tract).

These results were remarkable, because, although 4.34 per cent conformed to the figures given generally for the incidence of intrarenal disease among hypertensive patients, the incidence of extrarenal urologic disease was about four times as high. These urologic conditions included[3] prostatic obstruction with or without complications in the upper urinary tract, 31 cases; chronic pyelonephritis with complications, 27; renal stone and complications, 18; prolapse of the uterus with hydronephrosis and infection, 7; diverticula of the bladder with complications, 5; urethral stricture (male), 4; cancer of the bladder with ureteral obstruction and infection, 2; renal tumors, 2; congenital cystic kidneys, 2; bladder stone, 1; congenital absence of kidney, 1; and vesicovaginal fistula, 1. Moreover, even this high figure, 101 cases, was conservative because many of the earlier cases lacked adequate urologic study. Pursuing this line of investigation further, we found,[4] in a series of 97 patients with prolapse of the uterus, frequently associated with bilateral hydronephrosis and infection, that 74 (76 per cent) had hypertension. This percentage was distinctly higher than would be expected from other studies[5] on the frequency of hypertension among hospitalized female patients in similar age groups.

During the progress of the investigation we found, in both the older and more recent literature, data which tended to confirm our suspicion that extrarenal lesions could cause hypertension. This suspicion is well

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Received for publication March 17, 1942.

justified from the standpoint of experimental physiologic studies, which reveal the existence of nervous and humoral mechanisms that are quite adequate to explain such a relationship in terms of renal ischemia. But to confirm the suspicion clinically would require more than the isolated instances (Ritch, et al.[6]) in which hypertension and urologic disease have been found in the same patient.

Even when large numbers of such instances are available for study, the evidence may remain inconclusive. Thus, 113 patients (45 per cent of a series of 250 cases of essential hypertension) were found by Schroeder and Steele[7] to have some form of organic renal disease. However, these authors state that many of these urologic conditions occur without hypertension, and vice versa: "Renal lesions associated with arterial hypertension have not been consistently found on postmortem examination, and the reason for this is unclear." Weiss and Parker[8] have reported that hypertension often occurs in pyelonephritis, and they estimate that 15 to 20 per cent of the cases of malignant hypertension originate with pyelonephritis.

Hines and Lander[9] found that urologic disease, regardless of type, had less influence on the incidence of hypertension than did a high normal blood pressure reading on the original visit, or a family history of hypertension. They conclude that "these data do seem to cast some doubt on the importance of renal disease in producing hypertension in the series as a whole and call attention to the importance of exercising caution in attributing a role of primary importance to a renal lesion simply because it is found in a patient who has hypertension."

Hypertension was present in 26.1 per cent of 180 patients with chronic bilateral pyelonephritis who were studied by Braasch and Jacobson;[10] the incidence was 6 per cent higher than that in a control group. These authors also reported that 75 per cent of the patients with hypertension had systolic pressures below 180 mm. Hg, which constitutes a relatively benign elevation.

Williams and Harrison[11] found and classified 30 renal lesions among 100 subjects with increased blood pressure. Pearman, Thompson, and Allen[12] found 205 instances of renal disease among 500 cases of hypertension which were studied urographically. Admittedly, this was a select group, for 397 of the 500 patients had abnormalities in the urine that directed attention to the urinary tract. Further analysis showed that surgical disease of the kidney was no more common than would be expected for any other chronic medical condition. The conclusion was reached that the coexistence of renal disease and hypertension does not indicate a causal relationship. Horton[13] reported that 40 per cent of 335 patients with hypernephroma had hypertension. Of 124 patients with other types of renal tumors, 57 had hypertension. In neither group was there a consistent alteration in blood pressure after removal of the tumor. This author concluded that the problem was not solved, even

though his study failed to substantiate the observations of others that the blood pressure fell after the removal of tumors. However, he admitted that, sporadically, some relationship seemed to exist.

Braasch, Walters, and Hammer[14] found that the incidence of hypertension in a group of 1684 patients "subjected to renal surgical operation was no higher than it was in a group of patients taken at random." Hypertension was present in 46.5 per cent of 43 patients who were operated upon for primary, atrophic pyelonephritis. It was observed 161 times (20.3 per cent) in 793 cases in which operation was performed for renal stone. These authors considered the role of infection to be most important.

Palmer, Chute, Crone, and Castleman[15] found that 22 per cent of 212 patients with a persistent elevation of blood pressure had urinary tract defects, as shown urographically. These authors considered these lesions to "represent a participating or precipitating, rather than a major, factor."

If there is any association between urologic lesions and hypertension it should be ascertained. Obviously, a single instance of bilateral or unilateral ureteral obstruction and recurrent infection, associated with hypertension, does not prove an etiologic relationship. In fact, when two conditions are individually rather frequent, they must occur together occasionally by pure chance. For this reason, the collection of a large number of coincidences of this sort in itself proves nothing. Therefore, since laboratory investigation was seriously handicapped by the chronicity of the processes concerned, we had hoped that other workers who had large series of cases available would publish their results. Since, however, upon retrospect, we found many cases in our series[2] that should have had additional studies for more complete diagnosis, it occurred to us that others may have had the same difficulty. In other words, although it is easy to publish a list of conditions, either assumed to be causal, or suspected to be from the fact that they occasionally occur in cases of hypertension, it is quite another matter to state the percentage of incidence of these various associated conditions and draw conclusions from these percentages. Thus many classifications have appeared[16] in the literature, culminating in the list of 47 associated conditions compiled by Page.[17] It was decided, therefore, that a statistical analysis of the problem, using autopsy material, would be desirable.

MATERIAL AND METHODS

To avoid the use of biased data we examined the post-mortem protocols of the Department of Pathology of Northwestern University Medical School. These autopsies were performed in numerous general hospitals, and should represent a fair cross section of the autopsied population of a large city. One hospital limited admissions to men, so that there is a preponderance of males (69 per cent) in the series. The survey covered, without interruption, a 10-year period from 1930 to 1939, inclusive, so that any seasonal effect upon the sampling process was avoided.

TABLE I

Showing the number of males and females for each 10-year age group of 1962 patients.

AGE IN YEARS	SEX	
	MALE	FEMALE
20-29	77	61
30-39	97	87
40-49	236	119
50-59	328	128
60-69	343	120
70-79	239	67
80-89	39	18
90-99	3	0
Totals	1362	600
Per cent	69	31

Since we were interested in the effect of chronic disease, we excluded subjects whose age was 19 or under. The ages ranged between 20 and 99 years, although only 3 members of the group reached the tenth decade. We recorded the highest blood pressure measurement which was available, and used, as a dividing line between high and normal, 140 mm. Hg for the systolic, and 90 mm. Hg for the diastolic. It seemed to us that many instances of hypertension might not be included, for patients who died of cardiac failure, or in shock as a result of myocardial infarction, surgical procedures, accidents, etc., or in cachexia (carcinoma, tuberculosis, etc.) might show low measurements during their terminal illnesses. Therefore, we included the weight of the heart, for an increase in the size of the left ventricle in the absence of valvular disease constitutes one of the criteria by which elevation of the blood pressure may be diagnosed at autopsy. We considered the normal weights to be 300 grams for males and 250 grams for females.[18] A 33⅓ per cent increase[19] in weight above these figures (400 grams for males and 333 grams for females) was regarded as evidence of hypertrophy. The presence or absence of valvular disease, etc., was carefully searched for and recorded. The term "urologic disease" was broad, including all the obstructions and infections or various combinations of these. In addition, gross congenital lesions (horseshoe kidney, renal aplasia, congenital cystic kidney, double pelves with hydronephrosis) were incorporated. Small, occasional cysts were excluded, as were all the usual forms of nephritis and nephrosis.

The total number of records surveyed was 2,002. Not all were complete from our standpoint, and the unknowns were left out of the final computations. We attempted to include these unknowns by prorating and adding them proportionately to the known. We found, however, that if we included the unknowns and distributed them according to an arbitrary scheme we could prove any desired hypothesis. If we distributed them according to probabilities we obtained a diluting or attenuating effect. Therefore, by omitting all unknowns and uncertainties we felt that factual statements concerning the data could be made.

The otherwise difficult tabulation of these records was facilitated greatly by the use of punch cards and sorting machines. To obtain information concerning the significance of our observations, we employed the four-fold table and the chi-square test, as recommended by Pearl.[20]

RESULTS

The results of the study have been arranged in four-fold tables, as illustrated in Table II. This is a summary of 1,179 patients. These were

TABLE II

Four-fold table showing the presence or absence of urologic disease, compared with the systolic blood pressure. The figures in the small boxes in the upper left-hand corner of each cell represent the theoretical frequencies. The others are observed frequencies.

UROLOGIC DISEASE	SYSTOLIC BLOOD PRESSURE		
	140 MM. HG OR OVER	139 MM. HG OR LESS	TOTALS
Present	190 | 227	204 | 167	394
Absent	378 | 341	407 | 444	785
Totals	568	611	1179
Chi-square = 21.11		Probability = 0.000007 (Significant)	

subdivided into two groups: 568 were classified as hypertensive, with blood pressure readings 140 mm. Hg or over; 611 had 139 mm. Hg or less. Each of these groups was further subdivided as to the presence or absence of urologic disease.

In the hypertensive group, 227 patients, or 40.0 per cent, showed definite abnormalities of the urinary tract, and 341, or 60.0 per cent, at subsequent autopsy, showed no urinary tract disease. Of the 611 patients with systolic pressures below 139 mm. Hg, 167, or 27.4 per cent, had urologic lesions, and 444, or 72.6 per cent, showed no such lesions. If this group was typical, the chances are two in five that a patient with high blood pressure has urologic disease.

Significant conclusions may be drawn from this table, inasmuch as it shows the observed frequency of the two factors under consideration, i.e., urologic disease and hypertension. In other words, given 1,179 patients, of whom 394 have urologic lesions and 568 have hypertension, a simple probability calculation shows that, as a result of mere chance, 190 patients will have both. Thus $(394 \times 568)/1179 = 190.0$ = theoretical frequency. The data show, however, that 227 patients were observed to have both conditions. Therefore, $227 - 190 = 37$ = the difference between the observed and theoretical frequencies. This means that there were 37 more people who had both hypertension and urologic disease than would be expected as a result of pure accident. This discrepancy between actual and theoretical frequency implies an association between hypertension and urologic disease. We confirmed this by the approved statistical procedure of the chi-square test which equals 21.11, which is large, and means that only 7 times in a million would so great a difference arise by accident. In other words, one may safely infer that a patient with hypertension is more likely to have urologic disease than is a patient without hypertension.

Any attempt to make the association stronger by using high diastolic pressures alone, or in combination with elevated systolic pressures, failed. Also, adding enlargement of the heart to the criteria for hyper-

tension did not result in a greater correlation. The systolic blood pressure alone would seem to be an adequate criterion for hypertension in this connection. Our tabulations on this point will form the basis of a subsequent report.

It is generally accepted that some elevation of blood pressure is concomitant with increasing age. It is also generally agreed that the incidence of urologic disease is higher in older people. Our analyses of these two points in these autopsies bear out the truth of these fundamental concepts. The question is to ascertain whether the introduction of the age factor would significantly alter the basic relationship of urologic disease and high blood pressure.

We constructed Table III, a sixty-four-fold master-table, to enable a number of smaller table break-downs to be developed. This introduces age and sex factors, and permits the segregation of young males with and without urologic disease and/or hypertension from any other age group.

TABLE III

Shows a break-down of the data on 1210 patients into a sixty-four-fold table, comparing sex, blood pressure, and urologic disease by age.

SEX—SYSTOLIC BLOOD PRESSURE—UROLOGIC DISEASE									
AGE IN YEARS	MALE				FEMALE				TOTALS
	140 OR MORE		139 OR LESS		140 OR MORE		139 OR LESS		
	PRE	ABS	PRE	ABS	PRE	ABS	PRE	ABS	
20-29	6	10	6	25	1	9	5	20	82
30-39	3	15	2	30	3	18	10	25	106
40-49	19	46	18	60	8	22	10	34	217
50-59	41	63	27	87	21	26	12	26	303
60-69	47	65	29	68	12	25	8	27	281
70-79	50	34	36	31	12	11	3	12	189
80-89	9	2	3	6	3	3	2	3	31
90-99	0	0	1	0	0	0	0	0	1
Totals	175	235	122	307	60	114	50	147	1210

TABLE IV

Shows the presence or absence of urologic disease and hypertension among 458 males between the ages of 20 to 59 years.

MALES AGED 20 TO 59 YEARS			
SYSTOLIC BLOOD PRESSURE	UROLOGIC DISEASE		TOTALS
	PRESENT	ABSENT	
140 mm. Hg or more	54 | 69	149 | 134	203
139 mm. Hg or less	68 | 53	187 | 202	255
Totals	122	336	458
Chi-square = 10.188		Probability = 0.0014 (Significant)	

Table IV shows that, of 458 males between the ages of 20 and 59 years, 69 had both urologic disease and hypertension. Theoretically, only 54 should have been found. Further, there were more persons with normal

blood pressures and no urologic disease than was theoretically possible. Chi-square equals 10.18, and the probability equals 0.0014. This is significant, and means that only 14 times in 10,000 would this relationship occur as the result of chance.

TABLE V

Shows the presence or absence of urologic disease and hypertension among 381 males between the ages of 60 and 99 years.

MALES AGED 60 TO 99 YEARS			
SYSTOLIC BLOOD PRESSURE	UROLOGIC DISEASE		TOTALS
	PRESENT	ABSENT	
140 mm. Hg or more	95 | 106	112 | 101	207
139 mm. Hg. or less	80 | 69	94 | 105	174
Totals	175	206	381
Chi-square = 5.154		Probability = 0.0232 (Significant)	

Among 381 males from 60 to 99 years (Table V), 106 were observed to have urologic lesions and hypertension, which are eleven in excess of the calculated number. Chi-square equals 5.15, and the probability is 0.0232, which is significant.

TABLE VI

Shows the presence or absence of urologic disease and hypertension among 250 females between the ages of 20 and 59 years.

FEMALES AGED 20 TO 59 YEARS			
SYSTOLIC BLOOD PRESSURE	UROLOGIC DISEASE		TOTALS
	PRESENT	ABSENT	
140 mm. Hg or more	30 | 33	78 | 75	108
139 mm. Hg or less	40 | 37	102 | 105	142
Totals	70	180	250
Chi-square = 0.728		Probability = 0.3953 (Insignificant)	

There were 250 female patients between 20 and 59 years of age in the group (see Table VI). Here there was an excess of three persons who were observed to have urologic lesions and hypertension. Chi-square equals 0.728, and the probability is 0.3953, which is considered insignificant statistically. Of 121 females between 60 and 99 years of age (see Table VII), 27 were observed to have urologic disease, whereas 22 was the theoretically possible number. Chi-square equals 3.769, and, from a statistical standpoint, the probability rests upon the borderline of significance, at 0.0524.

Table VIII includes 97 males between 20 and 39 years of age. Nine were observed to have hypertension and urologic disease, whereas the

TABLE VII

Shows the presence or absence of urologic disease and hypertension among 121 females between the ages of 60 and 99 years.

FEMALES AGED 60 TO 99 YEARS			
SYSTOLIC BLOOD PRESSURE	UROLOGIC DISEASE		TOTALS
	PRESENT	ABSENT	
140 mm. Hg or more	22 | 27	44 | 39	66
139 mm. Hg or less	18 | 13	37 | 42	55
Totals	40	81	121
Chi-square = 3.769		Probability = 0.0524 (Insignificant)	

TABLE VIII

Shows the presence or absence of urologic disease and hypertension among 97 males between the ages of 20 to 39.

MALES AGED 20 TO 39 YEARS			
SYSTOLIC BLOOD PRESSURE	UROLOGIC DISEASE		TOTALS
	PRESENT	ABSENT	
140 mm. Hg or more	6 | 9	28 | 25	34
139 mm. Hg or less	11 | 8	52 | 55	63
Totals	17	80	97
Chi-square = 2.812		Probability = 0.0939 (Insignificant)	

expected number would be only six. Chi-square equals 2.812, and the probability equals 0.0939, which is significant.

In spite of the fact that the most significant associations occurred in male patients, it is noteworthy that in every group, whether male or female, young or old, the number of patients who had the combination exceeded the theoretical expectation. We feel that this is significant from a practical standpoint.

DISCUSSION

The purpose of this report is to answer the question whether or not urologic hypertension exists as an entity. "Organic" and "renal" hypertension have been suggested as alternative names for this condition. The word "organic" would include any demonstrable pathologic change which might cause hypertension (i.e., adrenal tumors, etc.) unless strict limitations were recognized and applied. The term "renal" would include the usual forms of nephritis. The term "urologic" would seem to be preferable because the lesions are definitely associated with the urinary tract; not entirely medical, nor yet entirely surgical, they result from infection, obstruction, or a combination of both.

To answer this question we studied 2,002 autopsy records on persons who were 20 or more years old. In the preceding statements the ref-

erence is, however, generally to less than 2,002 cases, because, in each table, before summarizing, we eliminated those cases in which a condition was not specifically stated to be either present or absent, and also those cases in which the blood pressure was not given in figures.

The results show that 40.0 per cent of patients with hypertension had urologic disease. This figure is higher than the estimated 30.0 per cent in our earlier studies. This means that 60.0 per cent of the hypertensive group had no evidence of urologic disease at autopsy. This large number has been noted by others, and has led some authors to assume that there is an unknown sensitizing mechanism for hypertension, which is set off only in certain susceptible people by the urologic disease. On the other hand, only 27.4 per cent of persons with no increase in blood pressure had urologic disease. This is difficult to explain, and is the reason for numerous statements that the relationship under consideration is incidental rather than causal.

However, since 37 more cases were observed than there should have been theoretically, and since this number was shown to be significant, it may be stated that there is a positive correlation between urologic disease and hypertension that is convincing statistically. The large size of the sample makes it extremely unlikely that the differences could have been due to chance. In other words, it may be inferred that a patient with hypertension is more likely to have urologic disease than is a patient without hypertension. Actually, limitations must be imposed, because all we have shown is that, out of 568 patients who died, were autopsied, and had blood pressures of 140 mm. Hg or over during life, 40 per cent showed anatomic evidence of urologic disease post mortem.

Any attempt to make the association stronger by using high diastolic pressures alone, or in combination with elevated systolic pressures, failed. Also, adding enlargement of the heart to the hypertensive group did not result in a greater correlation. Using two criteria complicated the situation and did not increase the predictable number of patients who would be found to have urologic disease. The systolic blood pressure seems to be an adequate criterion for hypertension. Including the diastolic pressure and/or cardiac hypertrophy is not only impractical clinically, but it obscures the logic, complicates the mathematics, and attenuates the statistical correlation.

The master table (Table III) is included for completeness. Many comparisons are possible from this complicated sixty-four-fold table. For any age group of either males or females we may make comparisons between the simultaneous occurrence of urologic lesions and hypertension. This was done in Tables IV, V, VI, VII, and VIII only with male patients who showed statistically significant associations. Still there were always more persons who had both urologic disease and hypertension than would be expected theoretically.

Therefore, it may be stated that urologic disease, as we have defined it, is more common in patients with hypertension than is to be expected as a result of mere chance. The combination is rather more frequent than the isolated case reports would suggest, and this would indicate that urologic hypertension exists as an entity.

In this cross section of the autopsied population of a large city there is the additional factor that many of these persons had not run the complete life cycle of the disease. If our interpretation is correct, namely, that the development of urologic hypertension is a slow process which depends upon many factors related to abnormal kidney physiology, undoubtedly many of the patients died from other causes before the hypertension could be demonstrated.

All types of urologic disease should be thoroughly investigated and treated in their incipiency, if for no other reason than to avoid the possible development of hypertension. In addition, all patients with hypertension should be investigated for urologic disease, even if, by the time hypertension is present, the urologic lesions as well as the hypertension may be irremediable.

SUMMARY

1. A survey of 2,002 autopsy records was made to ascertain the relationship between urologic lesions and hypertension.

2. Statistical methods show that a patient with hypertension is more likely to have urologic disease than is a patient without hypertension.

We wish to express our appreciation to Dr. J. P. Simonds, who permitted us to study the records of the Department of Pathology, and to Mr. Kenneth W. Revell, of the Regional Tabulating Unit, Division of the U. S. Public Health Service, for Tabulating the results.

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EVALUATION OF HEART SIZE MEASUREMENTS

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DIAGNOSTIC study of the heart seeks to ascertain whether heart disease is present, and, if so, to establish its etiology and severity. It is an aphorism that an enlarged heart is an abnormal heart, and, beyond indicating the presence of disease, the recognition of enlargement provides valuable information as to the type and the extent of the lesion, for characteristic changes frequently occur in various types of heart disease. Accurate estimation of the size of the heart, therefore, is most important. Methods for studying the size of the heart include physical examination, techniques employing the roentgen ray, and the electrocardiograph. The x-ray and the electrocardiograph are precision methods, but it does not follow, as is frequently assumed, that the information they convey is, therefore, necessarily exact. For the proper interpretation of roentgenograms and electrocardiograms, a knowledge of valid criteria for evaluating the size of the heart is essential, as well as an appreciation of certain physiologic and technical considerations.

PHYSICAL EXAMINATION

Recourse to the more specialized techniques is not always feasible, and careful physical examination usually enables one to make an approximate estimate of the size of the heart. It should be recognized, however, that there are serious limitations to inspection, palpation, and percussion, particularly when the chest wall is very muscular or obese, or in the presence of pendulous breasts or emphysema. When the apical impulse is palpable, the size of the left ventricle may be estimated from the relation of the leftmost point at which a definite forward lift is felt[4] to a perpendicular dropped from the midpoint of the clavicle. The left nipple line is less dependable as a reference point because its position is variable; it may be situated well outside the midclavicular line in sthenic and obese male subjects, as well as in females. The left ventricle enlarges downward as well as to the left, particularly when aortic insufficiency is present, and may extend to the sixth intercostal space and yet remain well within the midclavicular line. Enlargement of the cardiac chambers other than the left ventricle cannot be detected on physical examination except in advanced stages. The right ventricle forms the anterior surface and lower anterior border of the heart, and, when enlarged, extends directly forward. Increased dullness to percus-

From the Diagnostic Laboratory, The Equitable Life Assurance Society of the United States.
Received for publication Feb. 26, 1942.

sion in the third left intercostal space and over the sternum at this level is suggestive of enlargement of the conus of the right ventricle. This portion enlarges somewhat earlier than the body of the right ventricle. Enlargement of the right ventricle may be evidenced by an accentuated epigastric pulsation, i.e., retraction of the upper epigastrium during systole. This must be interpreted with caution, however, for the epigastric pulsation may be prominent normally in subjects of thin build or when the heart is overactive.

The right border of the heart is formed by the right auricle, and dullness to percussion which extends definitely beyond the right sternal border suggests enlargement of this chamber. The area of cardiac dullness may extend to the right of the sternum, however, as a result of displacement of the right auricle by enlargement of the other cardiac chambers, or because of pericardial effusion, so that this sign is not specific of right auricular enlargement. Nevertheless, enlargement of the right auricle may be considered to be present when, in addition to increased dullness beyond the right sternal border, there are peripheral signs of congestion, such as hepatomegaly and increased venous pressure. In the presence of pericardial effusion the right cardiac contour may be distinguished by means of an overpenetrated roentgenogram made a few seconds after an intravenous injection of diodrast, which outlines the right auricle within the pericardial effusion. Even the left atrium may form the right border of the heart when it is markedly enlarged, and, in cases of giant left auricle, comes to occupy the greater part of the right lower thoracic cavity. This is apparent not only on percussion, but frequently as a visible and palpable systolic heave of the right anterior chest wall caused by systolic distention of the massive atrium as a result of the free mitral regurgitation which is usually present. Lesser degrees of enlargement of the left atrium cannot be detected by physical examination, for this chamber extends posteriorly in the earlier stages of enlargement. Straightening of the upper part of the left border of the heart, although a relatively early sign of left auricular enlargement, as well as an indication of right ventricular enlargement, cannot be reliably discerned by physical examination.

ROENTGENOLOGIC METHODS

Less stress is placed on the estimation of the size of the heart by physical examination than formerly, for roentgenologic methods directly visualize the cardiac silhouette and permit detailed study of the size, shape, and position of the heart. Fluoroscopy, technically the simplest of the roentgenologic procedures, as well as the most generally available, provides the greatest information, and should be carried out routinely as a preliminary to further roentgenologic study. In any study of the size of the heart an attempt should be made to describe enlargement in terms of the individual chambers, for characteristic changes occur in

various types of heart disease. For this purpose fluoroscopy is of particular advantage because the contours of the separate chambers may be inspected in their entirety by rotating the subject into oblique positions, and their limits ascertained by observation of the pulsations. Adequate visualization of all the chambers is afforded by making roentgenograms in the posteroanterior, left anterior oblique (50° to 55°), and right anterior oblique (50° or over), or right lateral, position (Fig. 1). Examination in the latter view is aided by outlining (not filling!) the esophagus with a thick barium mixture, for the esophagus is in close relation to the posterior surface of the heart, particularly the left atrium.

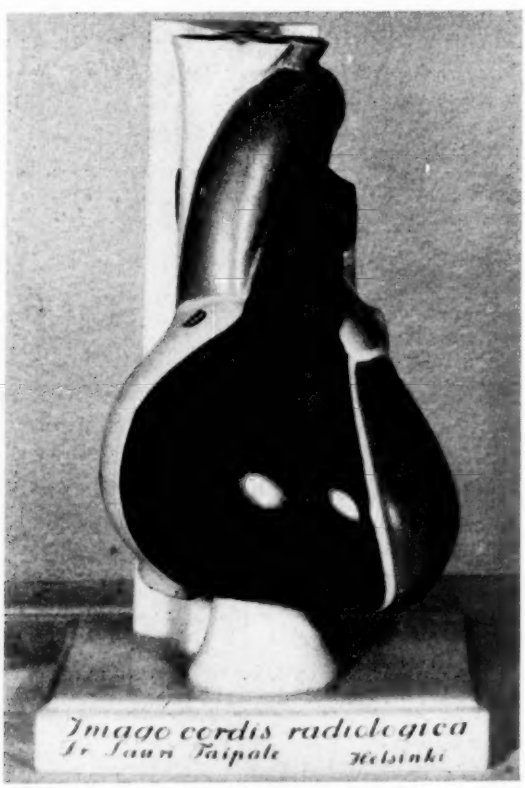
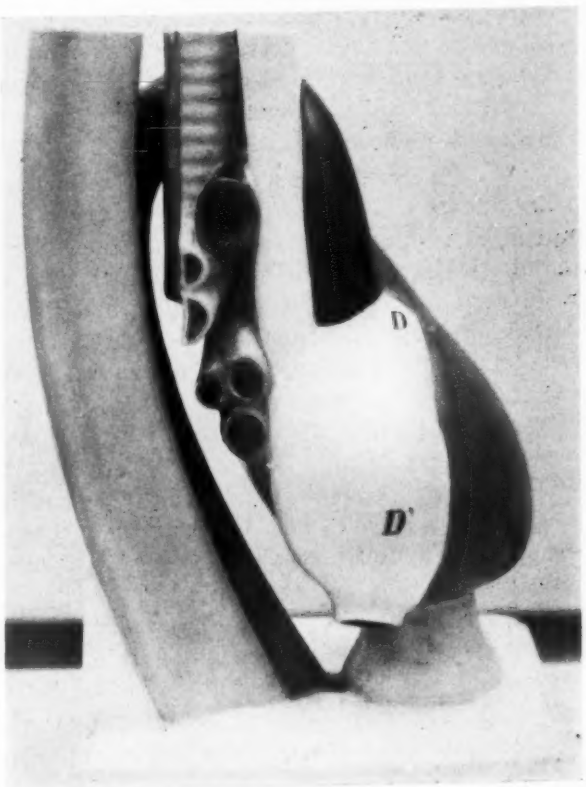


Fig. 1.—Positions for roentgenologic examination of the heart. *A*, Postero-anterior; *B*, left anterior oblique; *C*, right lateral.

The relation of the chambers of the heart to adjacent mediastinal structures, such as the esophagus, bronchi, and chest parietes, which can be ascertained by study in the oblique positions, is of great value in establishing whether or not enlargement is present. Thus, early enlargement of the left atrium is indicated by indentation and retrodisplacement of the esophagus, and also by upward extension of the left atrial contour toward the left main bronchus, which eventually becomes elevated and even compressed. The right ventricle forms the anterior sur-

B.



C.

face of the heart, and, when it is enlarged, extends forward toward the anterior chest wall, narrowing the precardiac space; this is revealed by study in oblique views.

Several measurements which purport to serve as criteria for enlargement of the individual heart chambers have been proposed.[5-7] Attempts to measure the size of the cardiac chambers separately are necessarily inexact, however, because only one border is visualized; the shadows of the various chambers merge to form the cardiac silhouette. Although the limits of the cardiac chambers may be recognized by the pulsations on fluoroscopic examination, they cannot be clearly distinguished in roentgenograms, and the applicability of such measurements is, therefore, greatly limited.

Measurements are of greater value as an index of generalized enlargement of the heart than in estimating the size of the individual chambers, and there is a definite field of usefulness for measurement standards in evaluating enlargement of the heart as a whole. Frequently, enlargement of the heart does not involve individual chambers distinctly, and one can state only that the heart is enlarged. Mensuration is unnecessary when gross enlargement exists, but lesser degrees of enlargement often escape detection on inspection. Conversely, an apparently large cardiac shadow may assume less significance when it is considered in relation to body build. If proper account is taken of the physiologic variables which influence the size of the heart, mensuration is a valuable aid in ascertaining whether the heart is enlarged. Measurements are valueless, of course, when the position and configuration of the heart are distorted by an unusually high position of the diaphragm or skeletal abnormalities of the thorax, such as scoliosis or funnel chest.

Most measurements refer to the frontal cardiac silhouette. It is important that the subject be centered properly, which can be recognized in the roentgenogram by equidistance of the inner borders of the clavicles from the midpoint of the vertebral column. The exposure should be made in the erect or sitting position, and with respiration suspended at ordinary inspiration, for extremes of respiration or straining may cause marked variations in the size of the heart. To minimize projection distortion, roentgenograms should be made at a 2-meter tube film distance (teleroentgenography). Fluoroscopy is not well suited for absolute measurement of the size of the heart, except when the orthodiagraphic technique is employed, for there is considerable magnification of the heart image caused by divergence of the x-ray beam as a result of the short tube film distance which is usually employed in fluoroscopic examination. Even at teleroentgenographic distance (200 cm.) there is a magnification, caused by projection distortion, of approximately 5 per cent; this does not increase appreciably until the tube film distance becomes less than 150 cm. When the tube film distance is shortened still further, as in fluoroscopy, the magnification may be estimated approximately, in subjects of normal build, as 1 per cent enlargement for

each 10 cm. less than 200 cm. The degree of magnification in the roentgenogram depends not only on the tube film distance, but also on the object film distance; and magnification is accordingly greater in subjects with deep chests, in whom the heart contours are further removed from the film, than in slender subjects and children.

TYPES OF MEASUREMENTS

Innumerable measurements have been proposed for the estimation of the size of the heart, and this has resulted in general confusion and skepticism about all measurements. Broadly, measurements of the heart are of three types: linear diameters, area of the frontal cardiac silhouette, and calculations of the heart volume. Three diameters, the transverse, longitudinal, and broad diameters, are best known, and these suffice for estimation of the size of the heart (Fig. 2), for not only have standards been established for them, but, in addition, the area of the cardiac silhouette and the heart volume may be calculated from these diameters with fair accuracy.

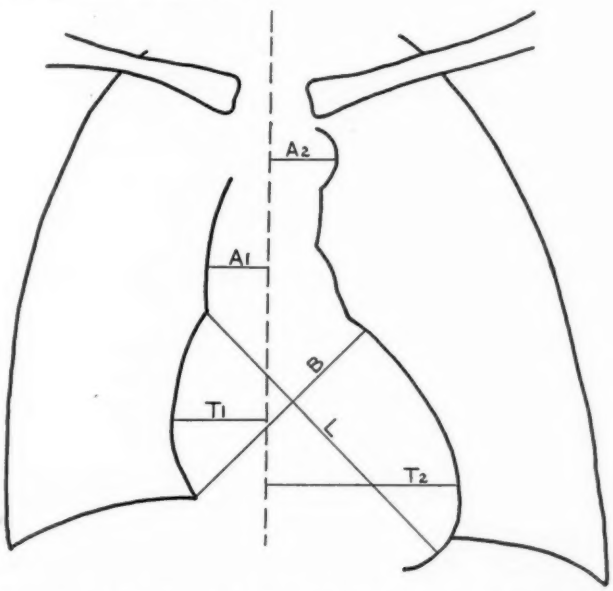


Fig. 2.—Diameters for measuring size of the heart: A_1 Plus A_2, transverse diameter of aortic arch. T_1 Plus T_2, transverse diameter. L, Long diameter. B, Broad diameter.

The simplest, most widely employed, and one of the most useful measurements is the transverse diameter, which is the sum of the greatest extension of the right border to the right, and of the left border to the left, of the midline. The cardiothoracic ratio, which is based on the assumption that the transverse diameter should be less than half the transverse diameter of the chest at the level of the diaphragm, has been widely popularized, but is crude and inexact. The width of the thorax is only a rough index of body stature, and is altered in any given case

by respiration, and also in pathologic conditions, such as emphysema. Ordinarily the transverse diameter of the heart is considerably less than half the transverse diameter of the chest, so that appreciable enlargement may escape detection if this ratio is employed as an index of the size of the heart. More accurate standards, based on weight and height, have been established both for the orthodiagram[8] and teleroentgenogram.[2] The influence of sex, and of age in adults, on the size of the heart is relatively small compared with the factors of weight and height, and, for practical purposes, may be disregarded in prediction standards. Teleroentgenographic standards are slightly greater than those for the orthodiagram, so that it is not proper to use the orthodiagram values in reading teleroentgenograms. Because of the increasing employment of the teleroentgenogram, a new prediction table, based on a study of 1,460 teleroentgenograms of normal subjects,[2] has been prepared, and this should be employed, rather than the older orthodiagram standards, when reading teleroentgenograms. A nomogram indicating the predicted transverse diameter from weight and height (Fig. 3) has been constructed.

The actual transverse diameter should not be interpreted too strictly in relation to the predicted value, for appreciable physiologic variations in the size of the cardiac shadow occur with respiration and changes from systole to diastole. Diameters which are more than 10 per cent above the predicted value should be regarded as abnormal, and the heart may be considered as almost certainly enlarged if the transverse diameter is over 15 per cent in excess of the predicted diameter. In measuring the transverse diameter, it is important to avoid including the extrapericardial fat pad which is frequently present, and which may merge with the lower portion of the left border of the heart. An increase in the transverse diameter is most often caused by enlargement of the left ventricle, but enlargement of any of the cardiac chambers, even of the left auricle, when it forms the right border of the heart, can widen the transverse diameter.

Two other diameters, the long and broad diameters, are well known, although these are somewhat less valuable individually than the transverse diameter. The long diameter extends from the junction of the cardiac and vascular silhouette on the upper part of the right border of the heart obliquely downward to the apex on the left. This diameter, which is approximately 10 per cent greater than the transverse diameter, is increased chiefly as a result of left ventricular enlargement. The broad diameter is the greatest diameter perpendicular to the long diameter. As a rule, it extends from the upper limit of the left ventricular contour to the lowermost point of the right border of the heart, but when the heart is of unusual configuration, the sum of the two greatest perpendicular extensions to the right and left from the long diameter is employed. If the heart is placed transversely, it may be necessary to extend the lower part of the right border slightly below the diaphragm

Nomograms for Area and Transverse Diameter of frontal heart silhouette

A. PREDICTED AREA FROM WEIGHT AND HEIGHT[1]; AND ACTUAL AREA FROM LONG AND BROAD DIAMETERS ($A = \frac{\pi}{4} L \times B$); FOR ORTHODIAGRAM AND TELEOROENTGENOGRAM.

B. TRANSVERSE DIAMETER OF HEART[2] AND AORTIC SILHOUETTE[3] PREDICTED FROM WEIGHT AND HEIGHT; FOR TELEOROENTGENOGRAM

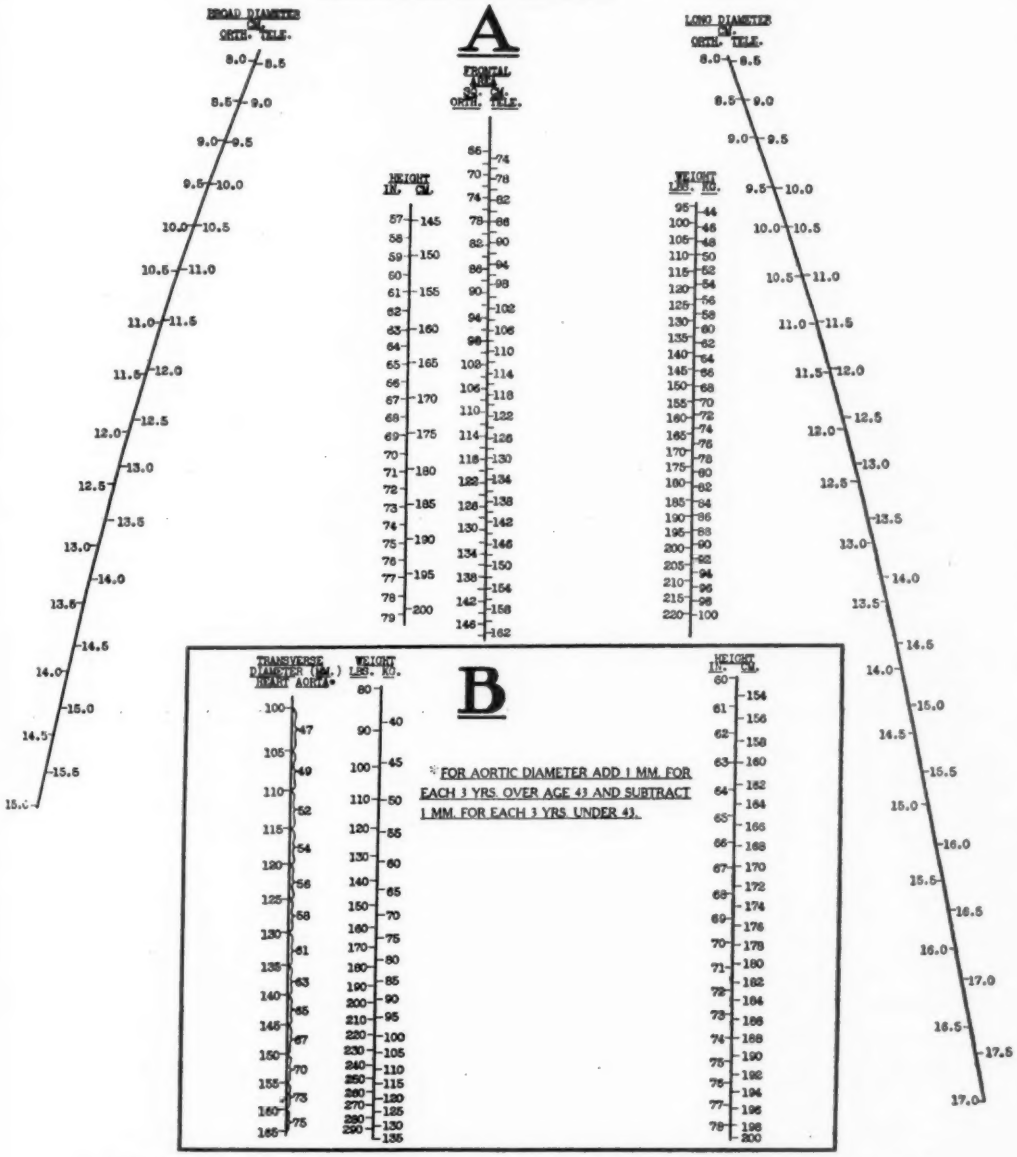

A
BROAD DIAMETER CM. ORTH. TELE.
LONG DIAMETER CM. ORTH. TELE.
FRONTAL AREA SQ. CM. ORTH. TELE.
HEIGHT IN. CM.
WEIGHT LBS. KG.
B
TRANSVERSE DIAMETER (MM.) HEART AORTA*
WEIGHT LBS. KG.
HEIGHT IN. CM.
* FOR AORTIC DIAMETER ADD 1 MM. FOR EACH 3 YRS. OVER AGE 43 AND SUBTRACT 1 MM. FOR EACH 3 YRS. UNDER 43.

Fig. 3.—Nomograms for frontal cardiac area, transverse diameter of heart, and aortic arch. The values for actual (or predicted) area are read at the point at which a straight line extending from the long and broad diameters (or weight and height) intersects the cardiac area scale. Orthodiagram values are on the left, teleroentgenogram values, on the right. In the lower nomogram the predicted transverse diameter of the heart (left side of scale) or aortic arch (right side of scale) is obtained as an extension of a straight line connecting height and weight. A correction for age, as indicated, is necessary for the aortic diameter. Values exceeding 10 per cent above the predicted for any of these measurements are abnormal.

in its natural curve in order to delineate the broad diameter. The broad diameter averages about 15 per cent less than the transverse diameter.

The long and the broad diameters are of interest, not so much by themselves, but for their product, which is an expression of the two-dimensional size of the cardiac shadow.[9] The product of these two diameters, which has been termed the heart rectangle, has been recommended as an index of the size of the heart in relation to the product of the height and width of the thorax.[10] This ratio is expressed as

$$\frac{\text{rectangle of heart } (L \times B)}{\text{rectangle of lung } (H \times W)}$$

Normally the ratio averages 23 per cent; it varies from 20 per cent in subjects of asthenic habitus to 26 per cent in those of stocky build. The heart is considered enlarged if the ratio exceeds 28 per cent. Although standards based on thoracic configuration are less accurate than those predicted from weight and height, this ratio is less open to criticism than the cardiothoracic ratio, in which only the width of the chest is considered. When the weight and height are not available, as is frequently the case in hospital studies, the ratio, $\frac{\text{heart rectangle}}{\text{lung rectangle}}$ is a suitable method for evaluating the size of the heart. An even simpler criterion, which is very satisfactory, is the relation of the lower part of the left border of the heart to a line dropped from the midpoint of the clavicle. Extension of the left border outside the left midclavicular line is usually indicative of left ventricular enlargement, and does not reveal changes in the other cardiac chambers, but it is the left ventricle which is most frequently enlarged in heart disease. This criterion has long been employed in physical examination, but serves equally well in roentgenologic study.[27]

CARDIAC AREA AND VOLUME

The area of the frontal cardiac silhouette in relation to standards based on weight and height has been widely recommended as an excellent criterion of the size of the heart.[1, 11, 12] In order to ascertain the area of the frontal silhouette, the upper and lower limits of the heart shadow must be completed by arbitrary and imaginary lines, and this requires considerable experience to attain duplicable results. The area is measured by means of a planimeter, or by counting squares within the area on cross-section paper. In orthodiagraphic examination, observation of the pulsations helps in outlining the contours. In the teleroentgenogram, however, the error in completing the upper and lower borders is much greater, and, for this reason, satisfactory frontal area measurements have not been obtained from the teleroentgenogram, although this method yields excellent results in orthodiagraphy in the hands of those who are well trained in the technique. Inasmuch as the cardiac shadow is ellipsoid in shape, its area may be calculated from

the product of its axial long and broad diameters (area of ellipse $=\frac{\pi}{4}$ long $\times$ broad diameters.)[9] Calculation of the cardiac area by means of the formula, $\frac{\pi}{4}$ long $\times$ broad diameters, yields values which correspond very closely to the actual area, as measured by planimetry.[13, 14] This product may, therefore, be used to estimate the cardiac area in lieu of planimetry. This is of particular advantage in the teleroentgenogram because the long and broad diameters can be measured accurately, whereas the planimetric estimation of the cardiac area is less accurate. The product, 2/3 long $\times$ transverse diameters, approximates the cardiac area, but is less satisfactory than the product of long and broad diameters, for the mean deviation from actual areas, as ascertained planimetrically in 134 orthodiagrams, was found to be 7 per cent, whereas with the long and broad diameter product the mean deviation in this group of 134 cases was less than 3 per cent. The predicted value for the cardiac area may be estimated approximately as follows: in a subject 5 feet 7 inches tall, weighing 150 pounds, the area should be 107 sq. cm. in the orthodiagram and 118 in the teleroentgenogram. One square centimeter is added for each 5 pounds over 150, and deducted for each 5 pounds under 150. Two square centimeters are added for each inch over 5 feet 7 inches, and deducted for each inch under 5 feet 7 inches. The actual cardiac area should not exceed 10 per cent over the predicted value, and, if it does, the heart may be considered as enlarged. A nomogram for prediction of the cardiac area from weight and height, and actual area as calculated from the long and broad diameters, are illustrated in Fig. 3.

The cardiac area is of great interest in another regard, in that it bears a close relation to the heart volume; the latter may be calculated from the cardiac area. In an extensive study on 62 cadavers, the area of the frontal cardiac silhouette was found to bear a close relation to the heart volume, and the formula, $V = 0.53A^{1.5}$, was proposed (where V = heart volume, A = area).[15] More recently a modification of this formula, $V = 0.63A^{1.45}$, has been recommended;[16] this yields values 6 per cent less than the older formula in the ordinary range of frontal area, varying from 90 to 130 sq. cm. Another formula for estimating heart volume from the frontal area is V = 0.36 long $\times$ broad $\times$ transverse diameters.*

*This is a modification of the Kahlstorf formula,[18] which has been widely recommended, but which requires study in the lateral as well as the frontal position.

$V = 0.63\ A \times T$, where V = heart volume
A = area of frontal silhouette
T = greatest horizontal anteroposterior diameter of the heart in the lateral position

The anteroposterior diameter of the heart may be estimated as 73 per cent of the frontal transverse diameter; in 150 cases it averaged 73 per cent, with a probable error of 6 per cent (calculated from data of Roesler, H. "The Relation of the Shape of the Heart to the Shape of the Chest," Am. J. Roent. 32: 464, 1934). Employing this ratio in place of the actual anteroposterior diameter, and the expression for cardiac area, ($A = \frac{\pi}{4}$ long $\times$ broad diameters), the formula becomes V = 0.36 long $\times$ broad $\times$ transverse diameters. In 104 cases, chiefly normal subjects, the mean heart volume, as calculated by this formula, was 680 c.c., whereas the mean heart volume as calculated by the Bardeen formula was 687 c.c. The average deviation of these two formulas was 41 c.c.

Several other methods which take into account measurements in lateral or oblique positions, in addition to the frontal views, have been suggested.[17-21] When the heart volume is estimated from teleroentgenograms, it is necessary first to correct the diameters for magnification (Fig. 3) before multiplying them to obtain the volume.

Although estimation of the heart volume is of great theoretical interest, the practical applicability is limited, particularly when study in more than one position is required. Apart from considerable variations in normal subjects, the volume varies from 25 to 30 per cent between systole and diastole, and the phase of the cycle must, therefore, be known. The volume during systole and diastole can be estimated by means of roentgenkymograms, but these are not generally available. The difference between the diastolic and systolic volumes, as measured kymographically, has been used to estimate cardiac output.[22, 23] The ratio, $\frac{\text{diastolic heart volume}}{\text{stroke volume}}$, which ordinarily varies from 7 to 10, is a direct expression of the efficiency and functional state of the heart in accordance with Starling's Law. This ratio is of greater significance than the heart volume or stroke volume alone, and any considerable increase betokens impaired cardiac reserve.[22, 24]

MEASUREMENT OF THE AORTA

Roentgenologic examination of the heart should invariably include the aorta, for abnormalities such as enlargement, tortuosity, and calcification occur very frequently in heart disease, particularly in hypertensive and arteriosclerotic heart disease and in syphilis. Measurement of the true caliber of the aorta is difficult because both contours are not visualized in the frontal position. The left border of the descending aortic arch is visualized in the frontal roentgenogram, and, if the esophagus is filled with barium, the right border of the aorta is indicated by the aortic indentation of the esophagus; therefore, the diameter at this level of the aorta can be ascertained.[25] The diameter of the transverse arch of the aorta can frequently be measured directly in the left anterior oblique position, particularly when some degree of emphysema is present to aid contrast, or when overpenetration technique is employed. These methods indicate the size of the transverse and descending aortic arch, but it is the ascending aorta which is most often enlarged in disease. The first portion of the ascending aorta is buried in the cardiac shadow, and cannot be studied by any means except contrast visualization with diodrast.[26] Enlargement of the ascending aorta is evidenced by prominence of the right border of the vascular pedicle, or by a forward bulge of the anterior border of the aorta, as observed in the left anterior oblique view. An increase in the transverse diameter of the vascular pedicle in the frontal roentgenogram does not specifically indicate enlargement of the aorta, for this may result from tortuosity alone; however, this measure-

ment is useful in that it does distinguish between a normal and abnormal aorta. In normal subjects the right border of the vascular pedicle is frequently formed by the superior vena cava, rather than the ascending aorta. In a recent study,[3] it was found that the transverse aortic diameter in normal subjects is closely related to weight and height. The table established for predicting the transverse diameter of the heart from weight and height may be employed equally well for the aortic diameter (Fig. 3). A correction factor for age is necessary; 1 mm. is added for each three years over the age of 43, and subtracted for each three years under the age of 43. Deviations from the predicted value up to 10 per cent are within allowable normal limits, but deviations in excess of this are infrequently seen,* and the aorta may be considered as almost certainly abnormal if the diameter exceeds 15 per cent above the predicted value, for 92 per cent of normal subjects fall within this range.[27] Although height, in conjunction with weight, is an important factor in predicting the transverse diameter of the heart, whereas age is of little consequence, this is not so with the transverse diameter of the aortic arch. In an analysis of 372 teleroentgenograms of normal subjects, the authors found that the correction for height between 59 and 76 inches was less than 1 mm., and height may, therefore, be disregarded. A prediction formula for the teleroentgenographic aortic transverse diameter is given by the equation, aortic transverse diameter (mm.) = 0.30 age, plus 0.14 weight (pounds), plus 23.86. This gives approximately the same values as those obtained by consideration of height, weight, and age. The transverse diameter of the aortic arch is a simple and valuable standard for measurement of the aorta. It is important that the roentgenogram be made with the subject properly centered, for even slight rotation into oblique positions markedly alters the aortic transverse diameter. If the diameter is found to exceed normal values, further study in the left anterior oblique position is indicated, for the aortic arch is best visualized in this view.

ELECTROCARDIOGRAPHIC SIGNS OF ENLARGEMENT

It has long been recognized that characteristic electrocardiographic patterns occur with enlargement of the cardiac chambers, but this aspect of electrocardiography has received relatively little attention. It is not generally appreciated that the electrocardiogram provides the most sensitive method for detecting hypertrophy of the left ventricle. Considerable hypertrophy may exist without any enlargement of the left ventricular cavity, the so-called concentric hypertrophy. Since hypertrophy may be a matter of an increase in thickness of the myocardium of only a few millimeters, this cannot be discerned in the

*In a series of 372 cases which were studied by the authors the actual aortic diameter was more than 10 per cent over the predicted in 17 per cent of normal subjects. Identical observations in a large series of cases were reported by H. H. Fellows, and also C. P. Clark (discussion of paper by Sheridan[3]).

roentgenogram unless associated enlargement of the cavity is present. Concentric hypertrophy may be suggested, however, by increased convexity of the left ventricular curve, even though the dimensions are not measurably increased. Hypertrophy of the left ventricle is usually accompanied by left deviation of the electrical axis in the electrocardiogram. This alone is of no diagnostic value, however, for it occurs in a very large percentage of normal subjects, particularly those who are heavy-set and have transversely placed hearts. Indeed, one reason for the occurrence of left axis deviation in most cases of hypertension is that the greater number of subjects with hypertension are of sthenic build, in whom left axis deviation occurs normally. Left axis deviation, therefore, cannot be considered indicative of "left ventricular preponderance," a term which has been used ineptly as synonymous with left axis deviation. Marked left axis deviation, when the QRS complex is inverted in Lead II as well as in Lead III, does not occur normally, but is caused by myocardial involvement rather than ventricular enlargement. This type has been termed pathologic left axis deviation.

Although left axis deviation itself is no indication of left ventricular hypertrophy, patterns occur which are characteristic of hypertrophy when left axis deviation is associated with other changes in the ventricular complex. An increase in the voltage of the QRS complex in the standard limb leads, most often in Lead I, occurs quite regularly with left ventricular hypertrophy. In an analysis of the electrocardiograms of 460 normal subjects with left axis deviation,[27] the voltage of the QRS complex was less than 1.56 millivolts in 95 per cent of cases, and the sum of the R wave in Lead I and the S wave in Lead III was less than 2.21 millivolts. In 99 per cent the voltage was less than 1.77 millivolts, and the sum of the R wave in Lead I and S wave in Lead III was less than 2.54 millivolts. These values were exceeded, on the other hand, in a very large percentage of cases of left ventricular hypertrophy. The sum of the R wave in Lead I and the S wave in Lead III was found to provide a somewhat more sensitive criterion of hypertrophy than the voltage in any one lead alone.

Characteristic changes occur, too, in the terminal deflections of the ventricular complex, and these may occasionally precede the increase in voltage. In Lead I the S-T segment becomes displaced below the isoelectric line, and there is a reciprocal elevation of the S-T segment in Lead III. In advanced stages the S-T segment may be depressed in Lead II, as well as in Lead I. It is generally stated that depression of the S-T segment is significant if it is more than 1 mm., but depression of any noticeable degree (0.5 mm.) in Lead I in association with left axis deviation must be considered significant because this was never observed in the series of 460 normal subjects with left axis deviation who were studied by the authors.

Flattening and subsequent inversion of the T wave in Lead I occur with left ventricular hypertrophy, and, in more advanced stages, inversion of the T wave occurs in Lead II, as well. There is a reciprocal relationship between the T wave in Leads I and III; as the T wave becomes deeply inverted in Lead I, it becomes more upright in Lead III. Normally, the T wave in Lead I should be at least 1 mm. in amplitude, and low amplitude in association with left axis deviation is suggestive of left ventricular hypertrophy.

It should be noted that the S-T segment and T-wave changes just described may be present with left ventricular hypertrophy in the absence of left axis deviation.[27, 28] This is particularly likely to occur in subjects of slender build. The changes in the S-T segment and T wave, although they are characteristic, are less specific for left ventricular hypertrophy than increased voltage, for they may occur in a variety of other conditions. In the more advanced stages of left ventricular enlargement, slurring, notching, and widening of the QRS complex are observed, and eventually the pattern of left bundle branch block appears. This is quite different in origin from the slight increase in the duration of QRS (up to 0.10 second) which may result from prolonged excitation of the ventricle caused by hypertrophy itself. It is most probably the result of the myocardial fibrosis which is generally associated with marked left ventricular enlargement, and which occurs chiefly in the subendocardial layers of the left ventricle and the interventricular septum, and therefore may involve the conduction system which ramifies in this region. In addition to the abnormalities described, changes in the precordial leads occur with both left ventricular hypertrophy and right ventricular hypertrophy.[29]

A characteristic electrocardiographic pattern occurs with hypertrophy of the right, as well as of the left, ventricle. The changes consist of right axis deviation, accompanied by depression of the S-T segment in Lead III and frequently Lead II, and inversion of the T wave in Lead III, and eventually in Lead II, as well. The voltage of the QRS complex is not regularly increased as it is with left ventricular hypertrophy. When the pattern is fully developed it is quite characteristic of right ventricular hypertrophy, but frequently in the less advanced stages it may be difficult to be certain that right ventricular strain is present because similar changes may occur in normal subjects of slender build, or as a result of positional changes of the heart. The electrocardiographic abnormalities frequently disappear in asthenic subjects, however, when the tracing is made in the recumbent position.

Auricular enlargement, also, may be revealed in the electrocardiogram. The left auricle is the one which is usually enlarged, most often because of mitral stenosis. Changes occur in the P waves as a result of impaired conduction through the dilated and hypertrophied auricle. The P wave

becomes notched, its duration exceeds 0.10 second, and it increases in amplitude to more than 0.25 millivolt. Ultimately, auricular fibrillation ensues as a result of longstanding auricular enlargement. Auricular premature beats and auricular flutter occasionally presage the change to auricular fibrillation. Although hypertrophy of the left ventricle may be detected earlier in the electrocardiogram, roentgenologic methods are superior in revealing auricular and right ventricular enlargement. When generalized cardiac enlargement is present the electrocardiographic changes are less specific, and the opposite effects of right and left ventricular enlargement may balance each other so that there is no deviation of the electrical axis, although other abnormalities, such as increased voltage and changes in the S-T segment and T waves tend to persist. The electrocardiogram may be relatively normal when enlargement is caused by dilatation of the cardiac chambers rather than by hypertrophy. Roentgenograms, therefore, are superior when generalized enlargement exists.

SUMMARY

Accurate estimation of the size of the heart is important. So far as possible, an attempt should be made to define enlargement in terms of the individual chambers, for characteristic changes occur in various types of heart disease. Enlargement of the cardiac chambers other than the left ventricle cannot be detected on physical examination except in advanced stages. Fluoroscopic or roentgenographic examination in frontal and oblique positions is of greater advantage in evaluating enlargement because the contours of the separate chambers may be visualized.

If proper account is taken of the physiologic variables which influence the size of the heart, mensuration is of value in ascertaining whether the heart is enlarged. Measurements are of greater value as an index of generalized enlargement of the heart than in ascertaining the size of the individual chambers. There is a definite field of usefulness for measurement standards in evaluating the size of the heart as a whole, for frequently enlargement does not involve individual chambers distinctly, and one can state only that the heart is enlarged. Mensuration is unnecessary when gross enlargement exists, but lesser degrees of enlargement often escape detection on inspection. Conversely, an apparently large cardiac shadow may assume less significance when it is considered in relation to body build.

The most practicable measurements are the transverse diameter and the area of the frontal heart silhouette. Planimetric measurement of the cardiac area is difficult and inaccurate in the teleroentgenogram, but the area may be calculated with considerable accuracy from the product of the long and broad diameters. A nomogram which enables one to calculate the frontal area from the long and broad diameters is presented. Predicted values for the frontal area from weight and height are shown

on the same nomogram, and, in addition, the predicted transverse diameter of the heart and of the frontal aortic arch silhouette are included. These measurements, i.e., the frontal area, the transverse diameter of the heart, and the transverse diameter of frontal aortic arch silhouette suffice for evaluating the size of the heart. Employment of the nomograms permits the convenient application of these more valuable cardiac measurements. Measurements are not to be regarded as final, but should be employed to complement careful study of the individual cardiac chambers by fluoroscopic examination; and the diagnostic significance of cardiac enlargement should always be considered in relation to the associated clinical observations.

Characteristic electrocardiographic patterns are observed when there is enlargement of the various chambers, and it is emphasized that the electrocardiogram provides the most sensitive method for detecting hypertrophy of the left ventricle. Roentgenologic methods are superior in revealing auricular and right ventricular enlargement, or when generalized enlargement exists. The electrocardiographic changes are the result of hypertrophy, rather than enlargement as such. The electrocardiogram may be relatively normal when enlargement is the result of dilatation without associated hypertrophy.

The authors acknowledge with thanks the aid of Mr. R. A. Porter, of the Statistical Bureau of the Equitable Life Assurance Society, in the preparation of the nomograms for the area and transverse diameter of the frontal silhouette of the heart.

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A SIMPLE METHOD FOR MEASURING CARDIAC AREA FROM THE ORTHODIAGRAM

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THE size of the heart is important in the diagnosis of heart disease. Of the available methods of estimating it, all of which are necessarily indirect, the area of the frontal projection of the heart's roentgenographic shadow is one of the most useful. The area of such an orthodiagraphic tracing, with the superior and inferior borders drawn conjecturally, is usually measured by a planimeter, or by transferring the outline of the area to finely squared paper and counting the squares contained within it. The latter method, to be accurate, requires finely squared paper and an estimation of how much of the squares which are transected by the cardiac outline should be included. Hence, it is tedious. The planimeter, although it is accurate and convenient, is not always available. It seemed desirable, therefore, to investigate the possibilities of a method which would not require the use of a planimeter and would avoid the tediousness and potential errors inherent in the squared paper method.

In 1914, Nissim[1] described a simple method for measuring the frontal area of the heart's roentgenographic shadow. The outline was traced on a sheet of aluminum which was cut out and weighed. The weight of one square centimeter of the aluminum sheet was also ascertained. The appropriate calculation gave the frontal area of the heart. A partial application of this method, in which paper was used instead of aluminum, was utilized by Strong and Gordon[2] to ascertain the effect of strophanthin on the size of the rabbit's heart. They did not actually measure the cardiac area, but used the method only for comparative purposes. They noted that A. E. Cohn had previously employed the same procedure.

METHOD

The method for measuring the area of the orthodiographic tracing which is described in this paper is essentially a modification of those mentioned above. The steps are as follows: The outline of the heart, with the superior and inferior borders drawn in conjecturally, is retraced on a piece of the same tracing paper which is used for the original orthodiagram. A sharply pointed grade 4 pencil has been found satisfactory for this purpose. The traced area is then cut out with scissors. The cutout is weighed on a chemical balance and its weight recorded. On another piece

From the Cardiovascular Research Unit, Veterans Administration.
Published with permission of the Medical Director of the Veterans Administration, who assumes no responsibility for the opinion expressed or the conclusions drawn by the author.
Received for publication March 9, 1942.

of tracing paper a square, 10 cm. × 10 cm. (100 sq. cm.), is drawn by means of a right-angled triangle and a centimeter rule. This area is cut out and weighed, and serves as a standard. Since the weight of 100 sq. cm. of the tracing paper and of the cutout which represents the cardiac area is known, the area of the cutout may be computed.

For example, the traced cutout of one orthodiagram weighed 362.5 mg. The average weight of 100 sq. cm. of the paper used in this study was 282.1 mg. One square centimeter of the paper, therefore, weighs 2.821 mg. Dividing the weight of the orthodiagraphic cutout by this factor gives a value of 129.2 sq. cm. for the area. Or, to put it in general terms,

$$\text{Area of cutout (sq. cm.)} = \frac{\text{Weight of cutout}}{\text{Weight of 1 sq. cm. of paper}}$$

Since the weight of the standard is a vital measurement which affects all estimations, it has been found desirable to ascertain the weight of an average standard from 10 to 12 separately measured squares. This value may be used in all subsequent estimations, but should be checked whenever a new roll of paper is employed.

Accuracy of Method.—The areas of 100 orthodiagraphic tracings and arbitrarily drawn areas of the shape of the heart were obtained by this method and checked by the planimeter. The average error for the 100 tracings was 2.8 per cent. The average negative error was 2.1 per cent; the average positive error, 3.2 per cent. Since the errors in the orthodiagraphic projection and tracing are greater than this, and since variations from normal of less than 10 per cent in cardiac area are not usually considered significant, it is apparent that this method is sufficiently accurate for all practical purposes.

Sources of Error.—The method has the following potential sources of error: (1) Variations in weight of paper; (2) errors in weighing; (3) errors in cutting outline; (4) errors in tracing.

An attempt was made to ascertain the magnitude of the variation in the weight of the tracing paper per unit area. Accordingly, 16 sheets of the paper were clipped together between sheets of thin cardboard with puncture clips. The tablet so formed was then cut into a roughly circular shape. By this means the errors caused by tracing and cutting the outlines were eliminated. The clips were then removed and the individual sheets weighed. The mean weight was 400.2 mg., with a standard deviation of ±10.4 and an average deviation from the mean of 2.1 per cent. Therefore, variations in the weight of the tracing paper are quite small.

The errors in weighing, likewise, are negligible. The weight of the traced areas of paper was of the order of 250-450 mg. Hence, an error in weighing of 1 mg. would at most introduce an over-all error of only 0.4 per cent. Although in this study the method of swings was used in the weighings, this is probably not necessary in ordinary routine work. The sensitivity of the average chemical balance is such that balancing the pointer within 3 scale divisions of zero will never introduce an error greater than 0.5 per cent.

No method was devised for differentiating errors in tracing and in cutting of outlines. However, in order to ascertain the constancy of the method without recourse to planimetric control, 12 separate tracings of the same original area were made. The mean area was found to be 132.8 ± 3.4 sq. cm. The average deviation from the mean was 1.9 per cent.

The magnitude of the possible errors in tracing and cutting may be estimated from a consideration of the shape of the orthodiagram and the formulas which describe areas of such shape. In general, the shape of the frontal projection of the heart approximates an ellipse, and at times approaches a circle. If, in tracing and cutting a circle 100 sq. cm. in area, the circle is cut 1 mm. larger than the original along its entire circumference (making a 2 mm. error in the diameter), the error in area will be 3.5 per cent. Similarly, in tracing and cutting an ellipse 107.0 sq. cm. in area, positive errors in the radii of 0.9 mm. and 1.2 mm. will introduce an error of 3.7 per cent. Experience has shown that errors as great as these are not likely to be made.

The errors of this method were more often positive than negative. Of the hundred estimations, 65 showed positive errors, as compared with the planimeter, with an average error of 3.2 per cent, whereas 35 showed negative errors, with an average of 2.1 per cent.

The accuracy of the method was, in our hands, improved by practice. In the first fifty estimations the average error was 3.7 per cent, whereas in the last fifty it was 2.0 per cent.

SUMMARY

A simple method for measuring the area of the orthodiagraphic tracing is described. It requires no instruments which are not already available in the average hospital. The error of the method is quite small, and well within normal variations in the size of the heart and errors in orthodiagraphic projection and tracing.

I am indebted to Blanche B. Wilcox, Ph.D., for the planimetric measurements.

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AN INTERPRETATION OF THE INJURY AND THE ISCHEMIC EFFECTS OF MYOCARDIAL INFARCTION IN ACCORDANCE WITH THE LAWS WHICH DETERMINE THE FLOW OF ELECTRIC CURRENTS IN HOMOGENEOUS VOLUME CONDUCTORS, AND IN ACCORDANCE WITH RELEVANT PATHOLOGIC CHANGES

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INTRODUCTION

CONSIDERABLE confusion and difference of opinion exist as to the interpretation to be placed upon the RS-T junction displacements caused by human and experimental myocardial infarction. For example, the prevalent idea that subepicardial damage produces an upward (positive) RS-T junction displacement and that subendocardial damage produces a downward (negative) RS-T junction displacement[1] is, in my opinion, clearly untenable. With certain reservations it may be admitted, in accordance with the opinion of others,[2] that the injury effects of infarction are brought about in essentially the same manner as those produced experimentally when the subepicardial region of the ventricular wall is damaged by heat, chemical agents, suction, or infection.

In the title of the present discussion the terms "injury" and "ischemic" refer to electrocardiographic effects, and have been defined in accordance with the membrane theory.[2-5] The difference between an injured and an ischemic zone of cardiac muscle is one of function with respect to the electrical effects which are produced. In this regard, an injured zone is one which acts during diastole, and probably during systole, as the source of an electrical field of injury, and is a zone within which there exists or appears to exist a gradient in the intensity of polarization. The injured zone is responsible for the RS-T junction displacements which appear on the completed record only during systole.[2] An ischemic zone is one in which polarization is everywhere complete during diastole (as in the case of normal muscle), but (unlike normal muscle) is one in which the onset of polarization is abnormally tardy during the regression period.[6] The existence of an ischemic zone of sufficient dimensions accounts for the primary T-wave changes which are occasionally observed before, and frequently after, myocardial infarction. Generally speaking, both an injured zone and an ischemic zone are regions which are deprived of their normal blood supply, and, therefore, both are ischemic, the former even more so than the latter. Nevertheless, it is of considerable importance from the electrocardiographic standpoint to differentiate the two zones in the manner described.

From the Department of Medicine of the Louisiana State University School of Medicine.
Received for publication, Feb. 26, 1942.

No demonstrable pathologic changes are implied by the ordinary use of the terms "injured zone" and "ischemic zone." As a matter of fact, local ventricular ischemia is known to be unattended by demonstrable structural change.[6] It seems possible that an injured zone may likewise be unchanged in the ordinary pathologic sense. By the time a region of cardiac muscle has suffered sufficient damage to exhibit microscopic changes, the involved cells have, it appears, already become electrically inert. These statements simply agree with the idea that a large gap ordinarily exists between delicate changes in a physiologic process and demonstrable pathologic change.

ON THE INCOMPATIBILITY OF DIRECT AND INDIRECT MYOCARDIAL DAMAGE

The injury effects of subepicardial damage produced by heat, suction, infection, or chemical or mechanical agents are almost certainly the result of the electrical activity of a thin layer of injured cells which separates the dead from normal (or the damaged from normal) muscle.[2] The injured layer acts during diastole as if it were an electric double layer in which a uniformly distributed source resides at that surface directed toward normal muscle and in which a uniformly distributed sink resides at that surface directed toward dead muscle.[2] It may readily be shown[7] by the laws which govern the flow of electric currents in volume conductors that the electrical field produced by an open double layer of the kind specified is proportionally represented by a single vector $\hat{i}$, the direction of which is that of a line drawn toward the center of the involved chamber normal to the plane circumscribed by the epicardial surface boundary of the double layer, and the magnitude of which is equal in units of length to the area of the plane in units of area. In recording the extremity leads (and unipolar leads), a current is introduced into the body-galvanometer circuit which neutralizes the effect during diastole of the diastolic field of injury.[3] If accession is regarded as a partial reversal of polarization, let us say to one-half of the intensity of the resting state, then $2/3\ \hat{i}$ is the effective electromotive force which is neutralized during diastole. Consequently, during systole, when the electrical field of injury again exists, with its polarity reversed, the neutralizing current is free to flow unopposed about the circuit, and the total effect on the completed record caused by injury is the same as if the field existed only during systole. That is, if the vector $2/3\ \hat{i}$ describes the field of injury during diastole, a vector $-\hat{i}$ must describe the effect on the completed record during systole. The vector $-\hat{i}$ may be termed the spatial axis of injury. The projection of $-\hat{i}$ upon the frontal plane of the body gives the vector $-\hat{i}$, which may be termed the axis of injury.

Of considerable clinical usefulness, because of its simplicity, is the triaxial reference system (Fig. 1*a*) formed by translating the sides *RL*, *RF*, and *LF* of the Einthoven triangle in such a manner that their midpoints meet in a common point at the origin *O*. The reference axes

thus formed have a positive and a negative half, divided by the origin *O*. The reference axes divide the frontal plane of the body into sextants. When the vector $-\hat{i}'$ is translated into the reference system in such a way that its origin coincides with the origin *O*, its projections $-\hat{i}'_1$, $-\hat{i}'_2$, and $-\hat{i}'_3$ upon the reference axes faithfully describe (in a proportional way) the RS-T junction displacements in the extremity leads. The subscript simply denotes the lead in question.

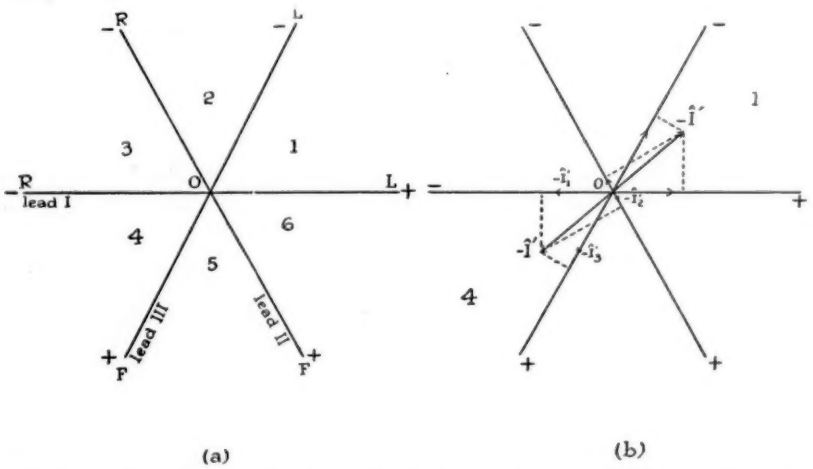

Fig. 1.—*a*, The triaxial reference system formed by translating the sides of the Einthoven triangle. The frontal plane of the body is thus divided into sextants. Sextants 5 and 6 are partially bounded by the positive half, and Sextants 2 and 3 by the negative half, of the three axes. Both sextants 1 and 4 are partially bounded by a positive and a negative half of the same two axes (Leads I and III). *b*, Showing the axis of injury $-\hat{I}'$, drawn outward from the origin O into the first sextant in order to represent the frontal plane projection of the spatial axis of injury $-\hat{I}$, which points from the center of the involved ventricle toward the center or centroid of an injured zone produced by localized pericarditis on the anterolateral ventricular wall. Also shown is another axis of injury $-\hat{I}'$, splitting the fourth sextant. By argument, the latter axis of injury is the one which should be produced by a subendocardial infarct in the same general location as the local pericarditis. The negative sign merely indicates that the quantity $-\hat{I}'$ is of the inverse direction during systole of the electromotive force of injury 2/3 $\hat{I}'$ which exists during diastole. When the vector $-\hat{I}'$ for either of the illustrated instances is projected, as indicated, upon the three reference axes, the resulting projections $-\hat{I}'_1$, $-\hat{I}'_2$, and $-\hat{I}'_3$ describe in both magnitude and sense the RS-T junction displacements of the leads denoted by the subscript. The projections are positive or negative (upward or downward) according to their location on a positive or negative half of the reference axes. See text.

For example, subepicardial damage caused by heat, chemical agents, suction, or infection, localized upon the anterolateral aspect of the left ventricle, produces an axis of injury $-\hat{i}'$ (Fig. 1, *b*) which splits the first sextant. Consequently, the RS-T junction displacements are of the discordant type, i.e., positive in Lead I, negative in Lead III, and variable in Lead II. On the other hand, subendocardial damage in the same general location is a structural inverse of the specified subepicardial damage, and should, by the same reasoning, produce an axis of injury $-\hat{i}'$ which splits the fourth sextant (Fig. 1, *b*). In this event the RS-T junction displacement should again be of the discordant type, i.e., negative in Lead I, positive in Lead III, and variable in Lead II. In spite of the fact that an infarct in the same general location in the left ventricular wall is ordinarily essentially subendocardial, these last men-

tioned effects are observed to be the inverse of those which are known to occur clinically and experimentally in association with anterolateral infarction. A similar disagreement exists also between the theory and actual facts pertaining to an essentially subendocardial infarct in other portions of the ventricular wall. The disagreement is likewise of an inverse kind for direct, semidirect, precordial, and esophageal leads. That most infarcts in man are essentially subendocardial is borne out by the significance in relation to infarction which has become attached to certain initial accession deflections (Q) of the extremity leads. Moreover, the transmural infarct almost always has an endocardial surface boundary which exceeds its epicardial surface boundary, with the result, according to the present argument, that its axis of injury should have a direction similar to that which would occur if the latter boundary were absent, as in the case of subendocardial infarct. Here again, the theoretical results prove to be the inverse of those which are actually known to occur with transmural infarction of various portions of the wall of the left ventricle. Inasmuch as the laws which govern the flow of electric currents in volume conductors have been adequately shown[3] to apply to problems of the kind under consideration, it follows that the situation which is known to exist after subepicardial injury produced by direct damage cannot be comparable in the details of its pattern to damage resulting from impaired coronary flow. Unlike direct myocardial damage, the damage resulting from impaired coronary flow is attended by a relatively widespread disturbance in the dynamics of local blood flow. The detailed pattern of this disturbance must, it seems, determine which zone will assume the injured state, and which will assume the ischemic state. The nature of the disturbance should also be reflected in the general character and distribution of the relevant pathologic changes. Dr. E. L. Burns* has kindly contributed the following summary of the anatomic changes:

The pathologic changes which occur in the heart of man and dog after rapid occlusion of a large coronary artery have been well described. Karsner and Dwyer,[8] working with dogs, studied the myocardial changes at various intervals after coronary artery ligation. They found that the affected areas of muscle first became cyanotic, and have an extremely irregular outline. Subsequently, the final area of infarction was observed to be considerably smaller than the early area of cyanosis. This was interpreted as indicating that, although the coronary arteries were terminal in an anatomic sense, there were probably rich possibilities for a collateral circulation. In early infarcts, congestion, hemorrhage, and edema occurred in the stroma, and cloudy swelling, fatty degeneration, and hyaline and granular necrosis occurred in the muscle fibers. After forty-eight hours, fibroblasts were numerous at the margins of the infarct, and contained occasional mitotic figures. Five days after infarction, the transition zone between

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necrotic and living heart muscle was demarcated by a well-defined zone of fibroblasts; and, after eighteen days, the infarcted area was composed of a well-formed scar. At this time the scar was fairly dense, moderately vascular, and contained remnants of hyalinized muscle. For the most part, living muscle ended abruptly at the edge of the scar.

The serial anatomic changes which follow infarction of the human myocardium have been well studied by Mallory, White, and Salcedo-Salgar.[9] The earliest changes, grossly, were pallor and dryness of the myocardium. In some instances, blotchy, red-purple areas of focal hemorrhage were found. These changes persisted and became accentuated during the first forty-eight to seventy-two hours. About four days after infarction, a fine yellow border could be seen at the periphery of the infarct. The yellow border proved to be a zone of leucocytic infiltration. By the six- to eight-day period, the zone of infiltration was broader, and, in some regions, was of a yellowish-green color. Eight to ten days after infarction, a reddish-purple zone, composed of newly formed capillaries filled with erythrocytes, had appeared at the periphery of the dead muscle. Concurrently, the volume of the infarct had contracted so that a definite, groove-like depression could be seen at its periphery. The depression had resulted from local removal of dead muscle fibers. By the end of three or four weeks, there remained only small islands of necrotic muscle, surrounded by granulation tissue. By the end of two or three months, the granulation tissue had become transformed into a white, fibrous scar. Whenever and wherever the epicardium or the endocardium was involved, simultaneous and similar changes occurred. Microscopic studies showed that myocardial necrosis was the earliest change, appearing within five or six hours after infarction. When the artery was completely occluded, uniform necrosis resulted. As a general rule, however, the necrosis failed to involve a thin layer of surviving muscle (0.3 to 0.5 mm. thick) which lay beneath the endocardium and extended within the wall along the thebesian veins of the involved region. Additional early changes included hemorrhage, fatty metamorphosis of the muscle fibers, and infiltration of polymorphonuclear leucocytes.

Microscopic evidence of healing commenced about the fourth day, at which time blood capillaries and fibroblasts had appeared at the periphery of the infarct and had begun to grow inward toward its center. Mononuclear cells (probably histiocytes) had begun to remove the necrotic muscle by phagocytosis. The latter process appeared to be progressing rapidly at the periphery of the infarct. By the tenth day, the necrotic muscle fibers had usually been removed completely from a zone 1 mm. wide at the margin of the infarct. Subsequently, removal of necrotic muscle took place more slowly, continuing to completion in about six weeks' time. At about the twelfth day, newly formed collagen fibrils were noted; by the end of the third week, collagen was moderately

prominent; and, by the end of the second or third month, the maximum amount of collagen had been deposited.

Mural thrombi were noted as early as the fifth day, and their organization was complete on about the sixteenth day. Recent or partially organized thrombi were sometimes found in association with relatively old infarcts, which suggested that thrombosis might have been caused by local dilatation of the heart wall, with resulting stagnation of blood in the neighboring portion of the ventricular cavity, rather than by any clotting effect exerted by the infarct itself. Moreover, a subendocardial layer of living muscle was frequently preserved beneath the mural thrombus.

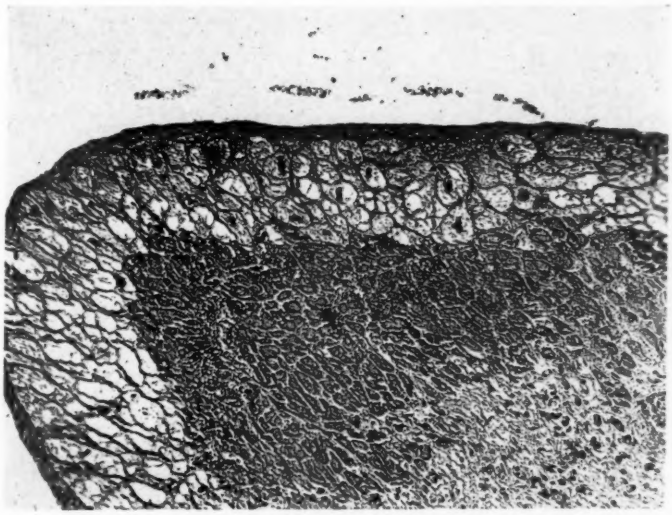

Fig. 2.—A section from the inner layers of the wall of the left ventricle. The patient had suffered from a growing infarct of three months' duration which measured 7 cm. in diameter. It involved the anterolateral wall of the left ventricle. The region shown is from the more recent basal zone of the infarct. The dark smooth margin is the endocardial surface. The subjacent region shows a distinct layer of living muscle. Note the gradient in its abnormal appearance which is everywhere more striking in a direction away from the endocardial surface up to the abrupt line where it terminates at the dark necrotic muscle. In the lower right-hand corner, the necrotic muscle has been partially removed. An electrocardiogram recorded on the day of the patient's death is shown in Fig. 3.

A comparison of the development and healing of myocardial infarcts in man and dogs shows many similarities and few differences. In dogs, hemorrhage is a more prominent feature, and the rate of healing is more rapid. Fibroblastic proliferation begins in about forty-eight hours in dogs, but requires about four days in man. In dogs, the dead muscle usually has been removed from a well-defined peripheral zone by the fifth day, whereas a similar process requires ten days in man. Scar tissue is well developed in dogs by the eighteenth day, but similar changes require two or three months in man.

The faster rate of healing in dogs has been attributed to the smaller size of the infarct and to a more normal residual coronary arterial tree.

In man, the residual coronary arterial tree is usually narrowed by atherosclerosis. A near certainty in man and a proved fact in dogs are the considerable extent to which the early zone of ischemia exceeds the final zone of infarction. The available pathologic evidence, therefore, suggests a general pattern similar to that shown in Fig. 4. On the other hand, Fig. 2 illustrates the surviving layer of subendocardial muscle which is observed in myocardial infarction in both man and dog. This section was obtained at necropsy from the heart of the same subject from whom the electrocardiogram (Fig. 3) was recorded.

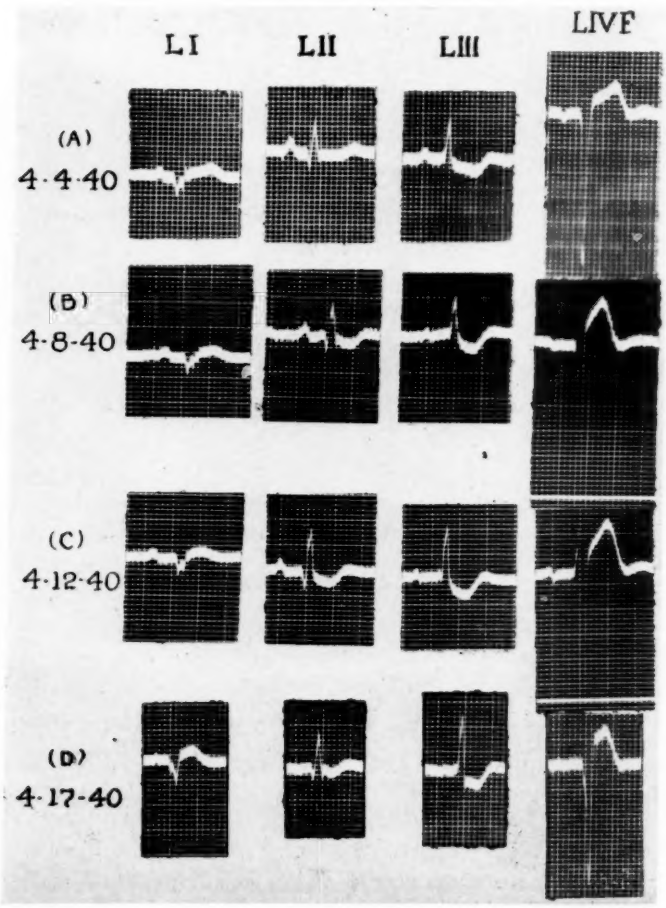

Fig. 3.—Curves A, B, C, and D are serial electrocardiograms recorded from a white male laborer, aged 42 years, who had been suffering from cardiac pain for three months. He had had high blood pressure for several years. The curves were considered diagnostic of fairly recent infarction of large dimensions involving the anterolateral wall of the left ventricle. Note the absence of R_1 and the growth of Q_1. Curve D, recorded on the day of death, shows a distinct injury current shift of the RS-T_4 junction. See legend of Fig. 2.

It has been suggested that this layer of subendocardial tissue survives because it receives nourishment from intraventricular blood by way of the thebesian veins. The layer or a part thereof often persists, however, even beneath a mural thrombus which makes nourishment by this route

impossible. In such instances it is probable that the layer continues to survive because it receives nourishment from a richly anastomosing plexus of arteries, described by Gross,[10] beneath the endocardial surface. In the absence of a thrombus the layer probably receives nourishment from both the thebesian veins and the subendocardial plexus of arteries, and in such cases the possibility of direct imbibition of oxygen from the neighboring ventricular cavity must also be considered.

THE ELECTRICAL REQUIREMENTS

In addition to the implications of certain of the above described pathologic changes are the requirements which may readily be deduced by a critical analysis of the electrical phenomena known to be associated with infarction. These requirements are: (1) The injured zone is, for the most part, a consistent feature of early infarcts. (2) The injured zone is located in the general region indicated by the spatial axis of injury $-\hat{\imath}$, which, by rule, points from the center of the involved ventricle toward the center or centroid of the injured region. (3) A corollary of Item 2 is that, if imaginary equipotential surfaces are constructed within the injured zone in such a way as to describe regions during systole throughout any one of which the intensity of incomplete polarization is everywhere the same, the surfaces must be more numerous between the dead zone and the endocardium than between the dead zone and the epicardium of an essentially subendocardial infarct (obviously, in a transmural infarct no such surfaces can separate the dead zone from the epicardium, for the two structures are contiguous). (4) The environment of the injured zone must be such as to enable the zone to continue electrical activity for several weeks in man (and for a more brief period in dogs). (5) The gradual disappearance of the activity of the injured zone must be intimately associated in some manner with, or be dependent upon, the appearance of the sequential and pronounced T-wave changes which are ascribed to perifocal ischemia. Finally (6), the injured zone must be so organized that it undergoes a subnormal change in the intensity of polarization. If the subnormal change occurs during regression of the injured zone, an injury current flows. If the subnormal change occurs during accession of the injured zone (a blocking effect), the field produced and its effects on the RS-T junction will be the same, or nearly the same, even though no injury current flows. It appears unlikely, however, that blocking occurs as a rule.

PROPOSED THEORY OF THE DISTRIBUTION OF INJURY AND ISCHEMIA

In a subendocardial infarct, the zone of injured cells which appears to meet the anatomic and electrical requirements is depicted in Fig. 4, *a*. The proposed theory of the distribution of the injured zone of a transmural infarct is shown in Fig. 4, *b*. The representations have been made highly diagrammatic for the sake of simplicity. As might be expected in the event that the infarct is essentially subendocardial, the injured zone is perifocal with respect to the dead zone. The ischemic zone, as

shown, is semiperifocal with respect to the dead and injured zones. For a transmural infarct, both the injured and the ischemic zones are depicted as semiperifocal with respect to the dead zone.

In Fig. 4, *a* or *b*, the lines drawn within the injured zone which commence upon the dead zone and cut the equipotential surfaces at right angles represent the imaginary paths along which the gradient of intensity of polarization increases most rapidly. They terminate upon the inner surface of the ischemic zone, where polarization is normal, and they terminate upon the neighboring epicardium. Presumably, after the early stages of infarction, the lines contract in the direction of the dead zone.

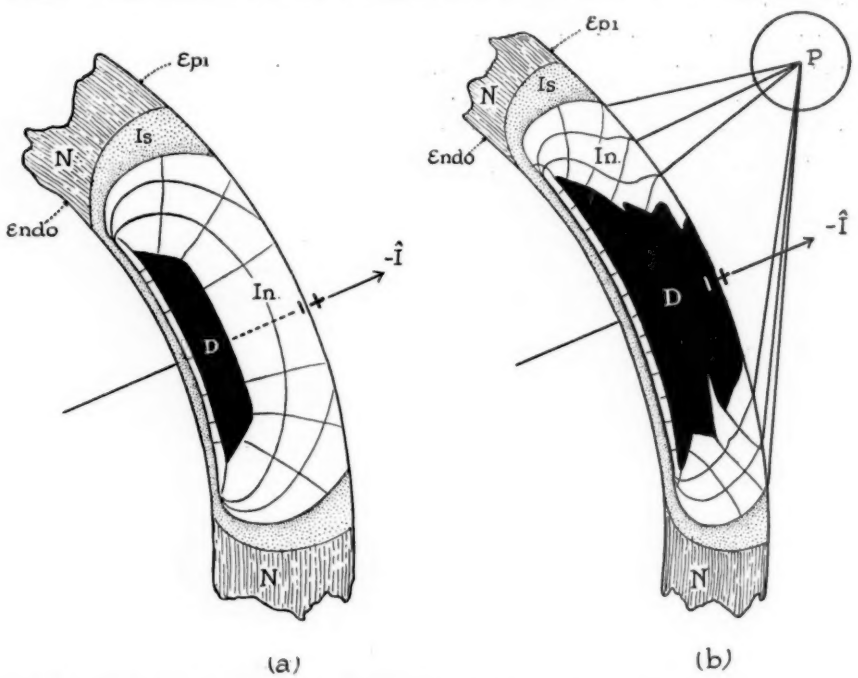

Fig. 4.—For either diagram, *N* is normal, *Is.* is ischemic, *In.* is injured, and *D* is dead, muscle. *a*, Showing the electrical situation as it apparently exists for recent, essentially subendocardial infarcts. *b*, Showing the electrical situation as it apparently exists for recent, essentially transmural infarcts. The equipotential surfaces which envelop or partially envelop the dead zones appear to make contact with one another in the subendocardial layer, whereas they are actually supposed to be separated by relatively small distances. Thus, the gradient of intensity of polarization increases very rapidly in the direction of the ventricular cavity, away from the dead zone. See text. For practical and theoretical purposes it is immaterial whether or not a part of the subendocardial layer persists, as shown, in the electrically ischemic state.

Thus, as the volume of the injured zone diminishes in the direction of the dead zone, the volume of the ischemic zone expands in a similar direction, for muscle units which are recovering from the injured state apparently pass into the ischemic state. When the length of the lines reaches zero, the injured state vanishes and the RS-T junction displacements disappear. Concurrently, as the initially small ischemic zone expands inwardly in a manner which increases its total volume, of necessity the related primary T-wave changes become progressively more pronounced.

Neither the equipotential surfaces nor the gradient of intensity of polarization is to be confused with the equipotential surfaces and the gradient of intensity of the electrical field produced by the injured zone. The former two terms are used in their broader sense merely to describe the source, not the distribution, of the field produced by the injured zone. The distribution of the source is lamellar. The distribution of the field throughout the heart and body may be likened (so far as the extremity leads are concerned) to that which would occur if an electric doublet were situated at the epicardial surface, with its axis collinear with the spatial axis of injury (Fig. 4). The injury potential at a field point p in the vicinity of the epicardial surface (Fig. 4, *b*) may be regarded as proportional to the sum of the solid angles subtended at p by the many epicardial surface boundaries of the open equipotential surfaces. On further analysis it becomes apparent that all regions enveloped by the closed equipotential surfaces make no contribution to the outside electrical field of injury. Moreover, when the injured zone is of such size and position as to be completely enveloped by the ischemic zone, all equipotential surfaces are closed, and no RS-T junction displacements occur. Clearly, the RS-T junction displacements of the kind under consideration are caused by greater injury at the epicardial surface than at the endocardial surface; that is, by a greater subnormal change in polarization on regression (or on accession, in the case of blocking) at the former than at the latter surface. The subnormal changes in polarization between the two surfaces are immaterial.

Frequently, the early QRS changes which are regarded as characteristic of infarction partially disappear. The disappearance is ascribed to diminution in the size of the injured zone, or, more properly, to the resulting increase in the strength of electrical forces which were previously weak during accession of the injured zone. The subsequent and often greatly delayed disappearance of the primary T-wave changes is ascribed to diminution in the size of the ischemic zone, a change which apparently depends upon further improvement in the local circulation. The subendocardial lamina of the damaged region (Fig. 4) is intimately associated with the Purkinje fibers within it. Consequently, accession of the lamina is insured, and this is an event which might be expected to produce a minute positive deflection at the onset of QRS in unipolar leads obtained by placing the exploring electrode superjacent to the infarct. Actually, minute positive deflections of the kind herein anticipated have been observed,[11] and their significance has hitherto been considered uncertain. A potential of this small order of magnitude is not ordinarily manifest in precordial leads. In man and dog, the frequent failure of infarction to produce appreciable prolongation of the QRS complex is regarded as indirect proof of accession of the specified subendocardial lamina.

The author sees no justification, as have some writers,[12] for ascribing any of the RS-T junction effects to a migration toward the ventricular

cavity of potassium which is supposedly released into the interstitial spaces of the infarcted region. If such a release actually occurs, the migration should be outward rather than inward; that is, in the direction of the decreasing gradient of intramural pressure. A phenomenon of this kind may help shape the injured zone into the configuration depicted in Fig. 4. On the other hand, the absorption of potassium could then determine, in part, the rate of diminution of the injured zone.

A NOTE ON THE RS-T JUNCTION DISPLACEMENTS AND SEQUENTIAL T-WAVE CHANGES IN ANGINA PECTORIS

The above described interpretation of the RS-T junction displacements and sequential T-wave changes caused by infarction has the additional advantage of being readily applicable to changes of a similar kind in curves recorded from certain patients during and immediately after attacks of angina pectoris. The involved region of the ventricular wall may be regarded as consisting initially of a relatively large injured, and a relatively small ischemic, zone. The injured zone may then be further described by means of equipotential surfaces to indicate regions throughout any one of which the intensity of polarization is everywhere the same during systole, and by lines indicating the direction along which the gradient of intensity of polarization increases most rapidly. These lines must commence at the point or points where the temporary deprivation of blood supply is greatest, and must end upon the inner surface of the semiperifocal ischemic zone, and upon the neighboring epicardium, and they must cut all encountered equipotential surfaces at right angles.

If one excludes the QRS changes which result from an alteration of position of the ventricular walls, or from an alteration in the manner of ventricular stimulation, those which appear during the anginal attack may be ascribed to the absence during accession of electrical forces which were previously present within the injured zone. As the injured zone diminishes and vanishes and the RS-T junction displacements concurrently disappear, the QRS changes likewise vanish. In a manner altogether similar to that described for infarction, the diminution of the injured zone contributes to the inward expansion of the ischemic zone. As each unit of muscle recovers from the injured state, it presumably passes into the ischemic state, for, within the injured muscle, the subnormal change of polarization which initially occurs during regression (or during accession if the case is one of local blocking) later becomes normal; whereas, there remains within the injured region a tardy onset of repolarization (ischemic state). An excellent example of the serial electrocardiographic abnormalities which are ascribed to these changes is depicted in a figure recently published by Wilson and Johnston.[13]

There is little doubt that the appearance in sequence of the RS-T junction displacements and the primary T-wave changes reflects a

fundamental law of dynamics of the disturbed myocardial blood supply. Until the pressure within the smaller subdivisions of the coronary circulation falls below that in the ventricular cavity as a result of local coronary obstruction, irrigation across the subendocardial lamina cannot take place. Irrigation of this kind from the ventricular cavity is necessarily confined strictly to the damaged region because the pressure gradients elsewhere are essentially normal. Moreover, irrigation from the ventricular cavity is probably limited primarily to the sphygmic period of systole, at least with lesser grades of local coronary obstruction. So far as the extremity leads are concerned, the electrical effects are adequately described by the development and the decay of the spatial axis of injury $-\hat{\imath}$, and by the sequential diversion and reversion of the gradient $\hat{A}_{QRST}$.[6]

A NOTE ON THE EFFECTS ON THE RS-T JUNCTION AND T WAVE OF PERICARDITIS ASSOCIATED WITH RECENT INFARCTION

There have recently appeared several admirable attempts[14, 15] to relate certain of the RS-T junction changes which occur with recent infarction to an associated pericarditis. Because of the complex nature of the problem, empirical as well as experimental studies are likely to lead to confusing results which are difficult to interpret and are of doubtful significance. However, clinical, experimental, and theoretical observations appear to be in agreement with the following comments. When there is a large, recent, transmural infarct of a region of the wall of the left ventricle which does not involve the apex, and when the associated RS-T junction displacements are concordant and positive in the extremity leads, the displacements must be ascribed chiefly to diffuse pericarditis involving the subepicardial muscle layer. If the specified variety of infarct has an apical location, RS-T junction displacements of the kind indicated must be ascribed to the semiperifocal zone of injury of the infarct, and not to a diffuse or local pericarditis. The epicardium over a transmural infarct is supported only by dead muscle which extends inward to the living subendocardial muscle layer, and, under the circumstances, the subepicardial reaction is electrically nil. In general, there is no sound clinical, experimental, or theoretical reason why any electrocardiographic changes should be ascribed to the strictly local pericarditis of a transmural infarct. If there is local pericarditis in the absence of an infarct, or, if a subendocardial infarct is present alone in the same general location, the RS-T junction displacements are similar. If a subendocardial infarct is associated with a superjacent pericarditis, the RS-T junction effects are cumulative. For any one of the three lesions, namely, a recent subendocardial infarct, a recent transmural infarct, and recent local pericarditis, the factor which determines whether the RS-T junction displacements will be concordant, discordant, or of some intermediate form is simply the location of the lesion.

The RS-T junction displacements caused by early diffuse pericarditis tend to obscure temporarily those produced by a recent "anterior infarct"; this statement should hold true in particular for the esophageal leads. The RS-T junction displacements caused by early diffuse pericarditis tend to obscure temporarily those produced by a recent "posterior infarct," especially in the precordial leads. A recent local pericarditis and a recent infarct which are located diametrically across the ventricles from one another tend to produce RS-T junction displacements which are inverse in the extremity leads and may thus nullify each other.

In uncomplicated diffuse pericarditis, the primary T-wave changes consist of concordant inversion. These are reasonably ascribed to the fact that the injured subepicardial zone subsequently acts as if it were ischemic. Intense, apical ischemia may produce the same kind of T-wave change, except that the Q-T interval tends to be prolonged.[12] However, to state that such T-wave changes are caused by extensive infarction[15] is both misleading and theoretically unsound. The association of such T-wave changes with the QRS changes caused by a small apical infarct suggests that the ischemic zone which produces the T-wave changes is semiperifocal with respect to the dead zone of infarct. If, on the other hand, the QRS changes are diagnostic of infarction in a location other than the apex, the specified T-wave changes are best regarded as indicative of the additional presence of apical ischemia or late diffuse pericarditis.

SUMMARY

1. There is a current difference of opinion regarding the interpretation to be placed upon the RS-T junction displacements caused by myocardial infarction.

2. When an electrical situation similar to that which exists with certain varieties of direct subepicardial damage is applied to the ordinary varieties of infarction, according to the laws which determine the flow of electric currents in homogeneous volume conductors, the predicted electrocardiographic effects prove to be the inverse of those which are known to occur clinically and experimentally in association with infarction.

3. Inasmuch as these laws have been shown to apply to problems of the kind herein considered with sufficient accuracy to be useful, it appeared highly probable that the electrical situations caused by direct damage and by infarction, although fundamentally similar, must differ considerably in pattern detail.

4. A summary of the pathologic changes is presented, together with the requirements deduced from a critical analysis of the electrocardiographic changes associated with infarction. The data led to a reasonable definition of the source and sink distribution of the electrical field

of injury and of the neighboring zone of ischemia which are associated with infarction. Moreover, an explanation for the occurrence in sequence of the RS-T junction displacements and the primary T-wave changes is regarded as an integral part of the problem. This sequential relationship, together with heretofore unexplained QRS changes, is thus accounted for incidentally. The RS-T junction displacements in the extremity leads are regarded as the result of the development and subsequent decay of the spatial axis of injury $-\hat{\imath}$. The primary T-wave changes have been ascribed elsewhere to a diversion and subsequent reversion of the spatial gradient of duration of the excited ventricular state. In general, the injured zone caused by recent infarction is perifocal or semiperifocal with respect to the dead zone, depending upon whether the infarct is essentially subendocardial or transmural. The ischemic zone is at first small and semiperifocal with respect to the injured zone. Later, as the injured zone diminishes in the direction of the dead zone and finally disappears, the ischemic zone necessarily undergoes an inward expansion and becomes directly perifocal with respect to the dead zone of a subendocardial infarct, or directly semiperifocal with respect to the dead zone of a transmural infarct. The changes are ascribed chiefly to improvement in the local circulation.

5. The explanation offered for the RS-T junction displacements and the sequential occurrence of T-wave changes as a result of infarction has the additional advantage of being directly applicable to similar but more transient serial changes which are observed in certain patients during and immediately after an attack of angina pectoris.

6. A summary of certain electrocardiographic interpretations is presented which is regarded as tentatively acceptable for curves that reflect the complex combination of infarction and pericarditis.

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ADDENDUM

While this article was in press, a report[16] of two cases of recent subendocardial infarction appeared. Because the extremity leads showed no RS-T junction displacements ascribable to injury, the infarcts were diagnosed as (and found to be) subendocardial. According to the material herein presented, this electrocardiographic feature is regarded as an indication that the infarct may be *strictly* anterior or posterior. The spatial axis of injury $-\hat{\imath}$, therefore, lies normal to the frontal plane of the body, and its projection upon the reference axes is zero. The remaining possibility is that the difference in the subnormal change of polarization at the epicardial and the endocardial surfaces is zero. Because the dead zone of infarction fails to involve the subepicardial muscle is not regarded as sufficient evidence for the diagnosis of subendocardial infarction. I have personally observed early anterolateral, as well as diaphragmatic, ventricular wall infarcts which produced the usual striking RS-T junction displacements and were subendocardial.

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THE INFLUENCE OF THE INDIFFERENT ELECTRODE UPON THE PRECORDIAL ELECTROCARDIOGRAM

I. The Normal Electrocardiogram

Hans H. Hecht, M.D., Eloise, Mich.

THE Committee of the American Heart Association on the Standardization of precordial leads[1] has left unanswered the question whether the position of the indifferent electrode has any bearing on the form of the precordial electrocardiogram, and did not decide which position is most desirable when recording chest leads. Various points on the body surface distant from the heart have been suggested previously as sites for the indifferent electrode (back, left arm, right arm, left foot, and others), and a number of studies bearing on their suitability have been carried out.[2-15] The work done thus far has not conclusively established that any one of these electrode positions is superior to the rest, but has shown that large differences in the resulting electrocardiogram may occur if the position of the "indifferent" electrode is changed while the precordial electrode remains in place.

Every electrocardiogram represents the resultant of the potential variations beneath the two recording electrodes, wherever they may be. This is true regardless of whether the electrodes are the apices of an equilateral triangle (standard limb leads) or whether one of them is in immediate contact with the heart (direct leads) or in the precordial region (semidirect leads). The potential differences in the immediate vicinity of the heart are considerably larger than those at a distance from it.[17] Consequently, when one electrode is placed very close to the heart or in contact with it, the position of the second electrode is of little importance as long as it is far from the heart. In leads from the chest wall, however, the potential variations of the exploring electrode are much smaller than in direct leads, whereas the potential variations of the distant electrode remain unchanged. Consequently, the distant electrode has a much greater influence upon the precordial electrocardiogram than upon the curves obtained by direct leads. The influence of the potential variations of the distant electrode upon the precordial electrocardiogram has occasionally been disregarded. The relations between the different kinds of chest leads in common use are illustrated in Fig. 1.

To eliminate the influence of the distant electrode upon the precordial electrocardiogram, Wilson and his associates[18] substituted for

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Aided by a grant of the A. Mendelson Memorial Fund, Detroit, Michigan.
Read before the First Annual Meeting of the American Federation for Clinical Research, Minneapolis, Minnesota, April 20-21, 1942.
Received for publication March 26, 1942.

a single electrode of this kind a "central terminal," connected simultaneously to electrodes on the right arm, left arm, and left leg. Mathematical calculations, based on the theory of the equilateral triangle, and experiments on animals and men have shown that the latter undergoes no large potential variations at any time during the cardiac cycle.[18, 19] It is held that electrocardiograms taken in this way represent the potential variations of a single electrode, namely, the exploring electrode on the precordium. The connections used are illustrated in Fig. 1, *D*.

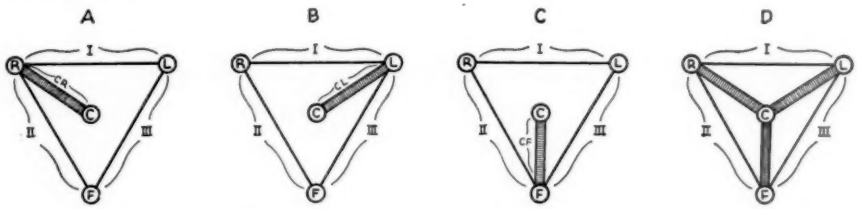


Fig. 1.—*L - R* represents Lead I, *F - R*, Lead II, *F - L*, Lead III.
In *A*: *C - R* are chest leads, using right arm as indifferent electrode.
In *B*: *C - L* are chest leads paired with left arm.
In *C*: *C - F* precordial leads with left leg as distant electrode.
In *D*: *C - (R+L+F)* are chest leads using Wilson's central terminal as second electrode. According to Wilson, Barker, and MacLeod *R+L+F = O*, if the heart is assumed to be the center of an equilateral triangle.

The differences between precordial electrocardiograms taken with different distant electrodes must depend upon the algebraic magnitude of the potential variations at the extremity upon which the "indifferent" or reference electrode is placed. Either calculation or actual recording of these extremity potentials is necessary in order to demonstrate their influence upon precordial leads. Both methods have been used. Recently, Wolferth and Wood[20] employed a method by which the influence of the indifferent electrode may be calculated from the standard limb leads. Wilson, Macleod, and Barker[21] have expressed the extremity potentials in terms of the electrocardiographic deflections of these same leads:

$$V_F \text{ (the potential of the left foot)} = \frac{\text{Lead II} + \text{Lead III}}{3},$$

$$V_L \text{ (the potential of the left arm)} = \frac{\text{Lead I} - \text{Lead III}}{3},$$

$$V_R \text{ (the potential of the right arm)} = \frac{-\text{Lead I} + \text{Lead III}}{3}.$$

Using these formulas, Wilson and his collaborators[21] and Kossmann and Rader[23] have, by calculation, freed their records of the influence of the distant electrode. With the introduction of the "central terminal" it became possible to record the potentials directly. Unipolar limb leads of this kind have been mentioned occasionally, but their importance in the solution of electrocardiographic problems has not been generally recognized. Their value in estimating the position and

movements of the electrical axis of the heart has been stressed by Kossmann and Johnston,[24] and Unghvary,[13] and lately by Wilson, Johnston, Cotrim, and Rosenbaum.[25]

The accuracy of these records of extremity potentials depends, of course, on the assumption that the "central terminal" is really a neutral electrode, i.e., does not undergo appreciable changes in potential. It has been pointed out that even though the sum of the potentials of the three extremities, when they are connected to the central terminal, may not always be zero, nevertheless the potential variations of the "central terminal" must be very small compared to those of any of the extremities alone.[26] Experiments by Eckey and Fröhlich[19] have shown that this conclusion is valid, and, in the case of normal subjects, the greatest potential variations of the "central terminal" do not exceed 0.3 mv. at any time during the QRS interval. For practical purposes, then, the "central terminal" may be regarded as neutral, and records taken with it represent a close approximation of the potential variations of the single electrode with which it is paired. A right arm—"central terminal" lead, for instance, records the potential variations of the right arm alone. It was thought that, by recording the standard limb leads, the extremity potentials (unipolar limb leads), and a number of precordial leads, the influence of the indifferent electrode upon the precordial electrocardiogram in leads CR, CL, and CF might be studied more satisfactorily than by any other method.

MATERIAL AND METHOD

Twenty normal persons (nurses, interns, attendants, draftees, and a few noncardiac patients from the hospital) were examined in this way, and the results have been analyzed and tabulated. All of the electrocardiograms which were obtained were normal. The subjects ranged in age from 11 to 62 years (average, 35 years). The tracings were recorded at 25 mm./sec. (standard speed), using a three-beam Sanborn electrocardiograph. Lead I was recorded simultaneously with each of the other leads. All tracings were taken with the subjects recumbent and relaxed. Thirty different leads were taken on each subject, as follows: (1) Three standard limb leads (0.1 mv. = mm). (2) Three extremity potentials (unipolar limb leads); the electrodes on the right arm, left arm, and left foot, respectively, were paired in turn with the "central terminal" in such a manner that an upward deflection of the string represented positivity of the extremity electrode (left arm wire on extremity electrode, selector switch in Lead I position). The deflections thus obtained are, on the average, about one half as large as deflections usually are in standard limb leads. The records were therefore taken with the electrocardiograph at twice the normal sensitivity (0.1 mv. = 2 mm).

(3) Serial chest leads were recorded from the six points recommended by the Committee of the American Heart Association on precordial leads.[1] Unless otherwise stated, the electrocardiograph was used at normal sensitivity. While the precordial electrode and the connecting wire remained in place, the wire connected to the other terminal of the galvanometer was connected in turn to the electrodes on the extremities and to the "central terminal." It would have been desirable to add to these leads one from the precordium to the back because some observers have placed the "indifferent" electrode in the left

scapular region. This was not done because it was thought undesirable to have the patient change his position. Possible effects of changes in position upon the position of the heart and upon the exploring electrode were thus avoided. Spontaneous changes in the electrocardiogram were ruled out by examining Lead I, which was always taken simultaneously with the other leads. Movements of the exploring electrode were avoided by using a special precordial electrode of the suction type.*

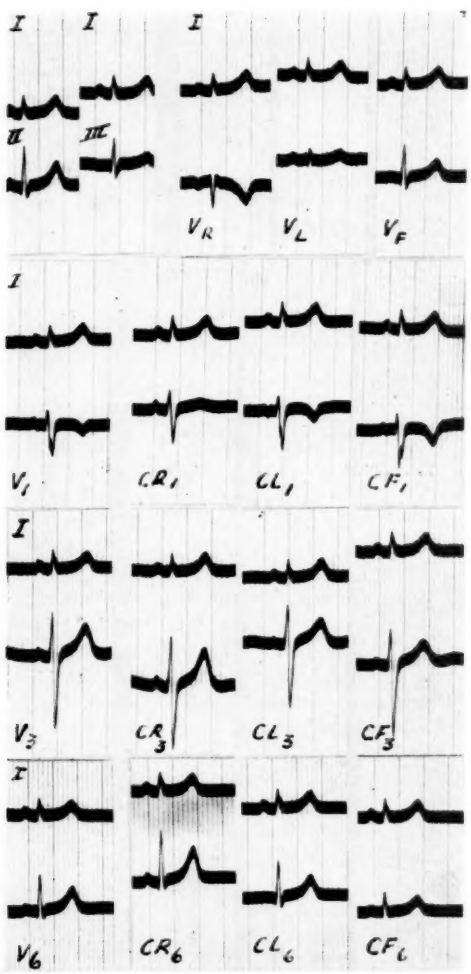


Fig. 2.—To conserve space only 3 of the 6 precordial leads which are recorded are reproduced (V_1, V_3, V_6). Miss J. L., 24 years of age, librarian. Normal axis position.

Top row: standard leads (N/sens.), extremity potentials (2N/sens.).

2nd row: leads from 4th intercostal space at right sternal border. Note upright *T* in *CR* (negative *T* in V_R) and markedly inverted *T* in *CF* (positive *T* in V_F).

3rd row: leads from 5th rib midway between left sternal border and left midclavicular line. Note large *P*, *T*, and *R* waves in *CR*, and deep *S* and relatively flat *T* in *CF*.

4th row: leads from 6th intercostal space in left midaxillary line. Note high voltage for all deflections in *CR*, and very small *QRS* and comparatively flat *T* in *CF*.

Lead I simultaneously, chest leads at N/sens.

*Manufactured by the Nichols Chase Company, Detroit, Michigan.

The electrode was 1½ inches in diameter. The suction was strong enough to keep the electrode in position as long as necessary, and its pressure was constant at all times. It was found that better contact was maintained with this type of exploring electrode by using an electrode jelly which did not contain the powdered pumice that is usually present in commerical preparations.

The "central terminal" was arranged as follows: Each extremity electrode was connected to an insulated wire of suitable length. The other end of each wire was soldered to one terminal of a 5000-ohm resistor. The unused terminals of the resistors were then soldered to a wire which was connected to the proper terminal of the electrocardiograph.[18]

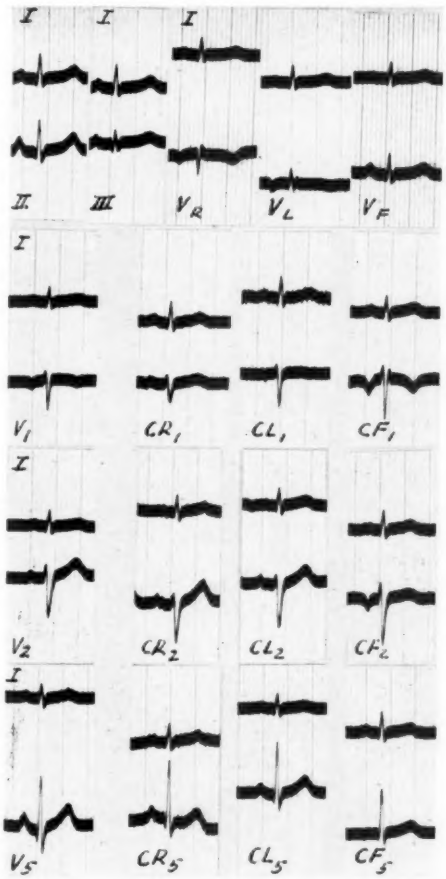


Fig. 3.—To conserve space only 3 of the 6 precordial leads are reproduced (V_1, V_2, V_5). Mrs. M. N., 52 years old, schizophrenia (untreated). Normal axis position.

Top row: standard leads (N/sens.), extremity potentials (2N/sens.).

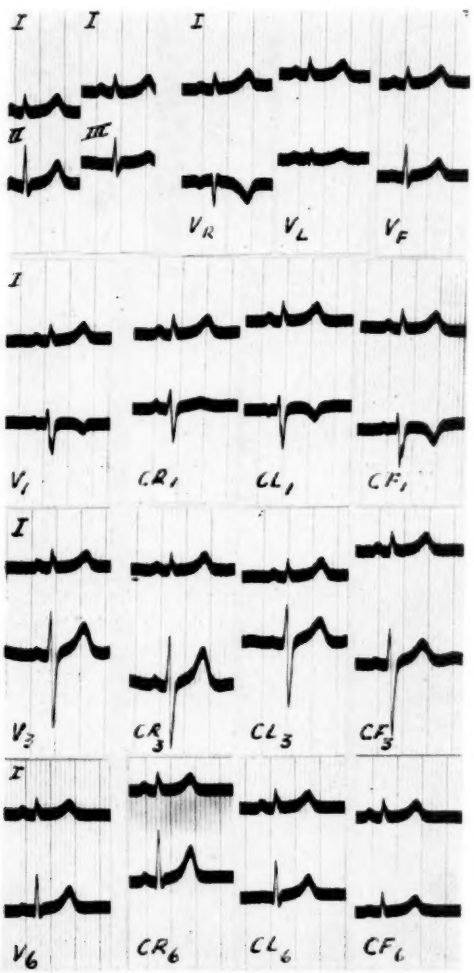
2nd row: leads from 4th intercostal space at right sternal border. Note marked inversion of *P*, *QRS*, and *T* in *CF* (positive *P*, *QRS*, and *T* in V_F) and upright *P* and *T* in *CR*, with low voltage of *QRS* (unfavorable lead).

3rd row: leads from 4th intercostal space at left sternal border. Note that large *S* waves and inverted *P* are still present in *CF*, together with flat but now positive *T* waves.

4th row: leads from 6th intercostal space in left anterior axillary line. Note isoelectric *P* in *CF*, together with small *S* (*S* wave present in V_F) and flat *T*. Large deflections in *CR*.

Lead I simultaneously, chest leads at N/sens.

scapular region. This was not done because it was thought undesirable to have the patient change his position. Possible effects of changes in position upon the position of the heart and upon the exploring electrode were thus avoided. Spontaneous changes in the electrocardiogram were ruled out by examining Lead I, which was always taken simultaneously with the other leads. Movements of the exploring electrode were avoided by using a special precordial electrode of the suction type.*



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Lead I simultaneously, chest leads at N/sens.

*Manufactured by the Nichols Chase Company, Detroit, Michigan.

The electrode was 1½ inches in diameter. The suction was strong enough to keep the electrode in position as long as necessary, and its pressure was constant at all times. It was found that better contact was maintained with this type of exploring electrode by using an electrode jelly which did not contain the powdered pumice that is usually present in commerical preparations.

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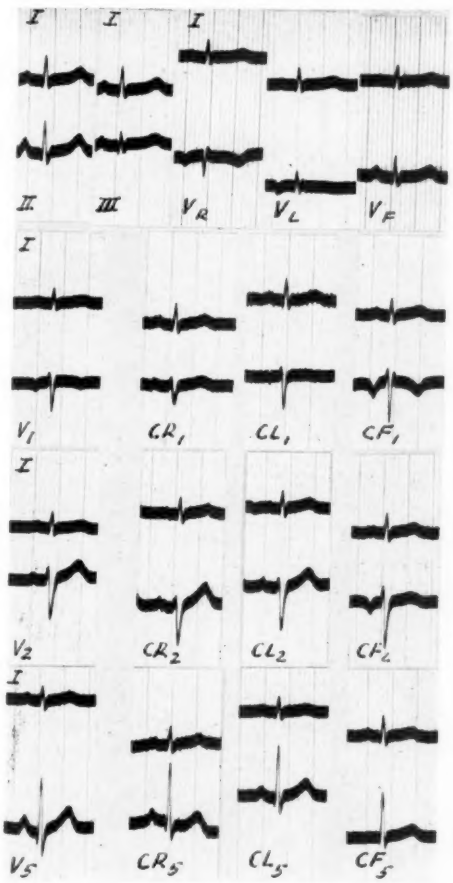

Fig. 3.—To conserve space only 3 of the 6 precordial leads are reproduced (V_1, V_2, V_5). Mrs. M. N., 52 years old, schizophrenia (untreated). Normal axis position.

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3rd row: leads from 4th intercostal space at left sternal border. Note that large *S* waves and inverted *P* are still present in *CF*, together with flat but now positive *T* waves.

4th row: leads from 6th intercostal space in left anterior axillary line. Note isoelectric *P* in *CF*, together with small *S* (*S* wave present in V_F) and flat *T*. Large deflections in *CR*.

Lead I simultaneously, chest leads at N/sens.

RESULTS

1. QRS complex.—In normal subjects the unipolar right arm lead (V_R) displays, during the QRS interval, a large downward deflection which is preceded or followed by a small positive deflection. The resultant QRS complex somewhat resembles that obtained from the right

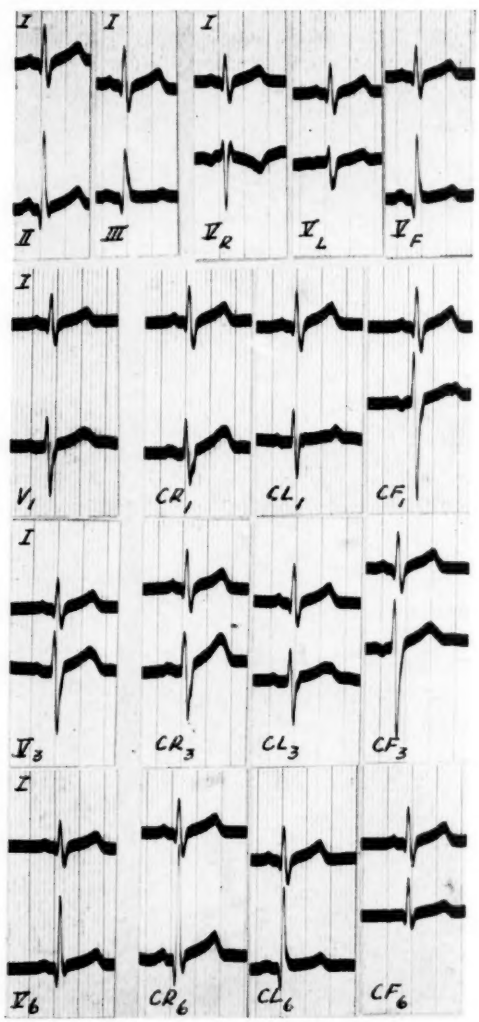

Fig. 4.—To conserve space only 3 of the 6 precordial leads are reproduced (V_1, V_3, V_6). Dr. B. Sh., 29 years of age. Tendency to right axis deviation.

Top row: standard leads (N/sens.), extremity potentials (2N/sens.).

2nd row: leads from 4th intercostal space at right sternal border. Note inverted *P* and large *S* in *CF* (positive *P* and large *R* in V_F). High amplitude in *CF* for all deflections, low voltage in *CR*.

3rd row: leads from 5th rib midway between left sternal border and midclavicular line.

4th row: leads from 7th rib in left midaxillary line. Note small total deflections for *QRS* in *CF*, with relatively large *S* waves (high *R* in V_F). Largest amplitudes in *CR*. Absent *S* in *CL* (large *S* in V_L).

Broad top of *S* waves in V_L results in slurring and notching of *QRS* in CL_1, CL_3, and CL_6.

Lead I simultaneously, chest leads at N/sens.

side of the precordium (Leads V_1, V_2), or that obtained in experiments on animals by leading from the ventricular cavities; the attachment of the right arm to the trunk is opposite the large valvular openings at the base of the heart, so that the negativity of the ventricular cavities is reflected to the extremity. The uniformity of the QRS pattern of V_R is apparent from the figures given in Table I. The QRS pattern of the left arm (V_L) and left leg (V_F) leads is much more variable. This was noted before by Kossmann and Johnston.[24] In our series of 20 cases, R varied in V_L from 0.03 mv. to 0.47 mv., and QS (the largest downward deflection—either Q wave or S wave), from 0.01 mv. to 0.56 mv.; R varied in V_F from 0.15 mv. to 1.12 mv., and QS from 0 to 0.15 mv. If, in extremity potentials, downward deflections represent the negativity of the endocardial surface or the ventricular cavities, upward deflections reflect the positivity of the epicardial ventricular surface.[25] The largest upward deflection is found in the lead from that extremity which best reflects the positivity of the epicardial surface of the heart, particularly of the left ventricular wall. In left axis deviation large R waves occur in Lead V_L, indicating that in this case the potentials of the left ventricular surface are transmitted to the left arm. In right axis deviation the left ventricular surface seems to face more toward the legs, and this would favor the appearance of large R waves in V_F. Marked left or right axis deviation is not observed in normal subjects, but normal curves often show features of the one or the other ("right types" and "left types").[26] The twenty normal subjects were divided into three different groups, as follows: 8 who showed a tendency to right axis deviation ($\alpha \sim 90°$), 8 who had no axis deviation ($\alpha \sim 60°$), and 4 who had a tendency toward left axis deviation ($\alpha \sim 30°$). As shown in Table I, the subjects in group $\alpha \sim 90°$ displayed large R waves in V_F, and ventricular complexes characterized by large negative deflections in Leads V_R and V_L. This suggests that the negativity of the base of the heart and the ventricular cavities is transmitted to both the right and the left arm when the heart is in a vertical position. The positivity of the epicardial surface of the left ventricle, on the other hand, is transmitted to the left leg (Fig. 5). In the group $\alpha \sim 30°$, large R waves occurred in Lead

TABLE I

THE VENTRICULAR DEFLECTION IN EXTREMITY POTENTIALS*
(IN TENTHS OF MV.)

	V_R				V_L				V_F			
	RS	R	QS	T	RS	R	QS	T	RS	R	QS	T
Group $\alpha \sim 30°$	6.94	0.96	4.06	−2.07	4.54	2.55	0.42	1.39	4.24	1.91	0.79	0.97
Group $\alpha \sim 60°$	4.42	0.42	2.69	−1.28	2.60	1.03	0.37	0.43	4.34	2.42	0.70	1.03
Group $\alpha \sim 90°$	5.92	1.01	3.60	−1.28	4.66	0.69	2.41	0.51	7.76	5.46	0.70	1.14
Total	5.76	0.80	3.45	−1.53	3.93	1.42	1.07	0.78	5.45	3.26	0.75	1.05

*To conserve space, neither range nor standard deviation is given for any of the data presented. This omission seems justified because the figures are presented as an illustration, rather than to state statistical facts. When it was necessary to give further detailed figures, the additional data are mentioned in the text.

V_L, which suggests that in this case the potentials of the left ventricular surface were transmitted to the left arm (Table I). As regards the average size of R in Leads V_L and V_F, the group $\alpha \sim 60°$ occupied an intermediate position. Although the different groups differed significantly with respect to the size of R and S in Leads V_L and V_F, the form of QRS in V_R was similar in all of them.

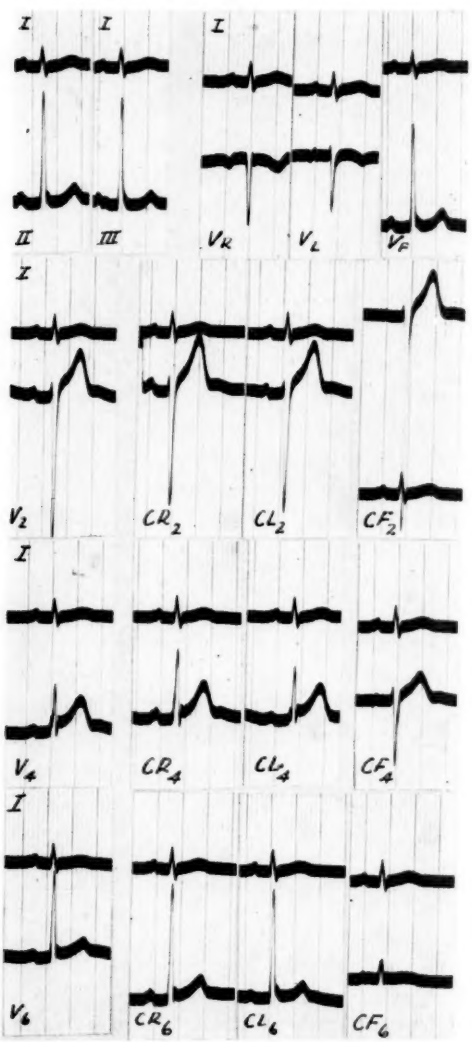

Fig. 5.—To conserve space, only 3 of the 6 precordial leads are reproduced (V_2, V_4, V_6). Dr. F. St., 27 years of age. Tendency to right axis deviation.

Top row: standard leads (N/sens.), extremity potentials (2N/sens.).

2nd row: leads from 4th intercostal space at left sternal border. Note marked increase in total amplitude of *CF* with large *S* waves (large *R* in V_F), and similarity of *CR* and *CL* (similarity of V_R and V_L).

3rd row: leads from 5th intercostal space in left midclavicular line. Note marked differences in direction of *QRS* in *CF*, as compared to other combinations (marked difference in V_F, V_R, V_L). High *P*, *R*, and *T* in *CR* (inverted *P*, *QRS*, *T* in V_R).

4th row: leads from 7th rib in left midaxillary line. Note abnormally small deflection in *CF* (marked distortion by large V_F).

Lead I simultaneously, chest leads at N/sens.

Table II indicates that CR leads yield higher R waves than the other leads, regardless of whether axis deviation is or is not present. In leads from the left side of the precordium (CR_5 and CR_6), all the deflections which are tabulated (RS, R, and QS) were larger in CR than in the other leads. This was true of each of the three groups. The potential of the right arm was negative throughout all but a small fraction of the QRS interval. The potentials of the right side of the precordium were predominantly negative, whereas the potential of the left side was positive. For this reason, Leads CR_1 and CR_2 yielded smaller deflections, and Leads CR_4, CR_5, and CR_6 yielded larger deflections, than the other chest leads. The average value of the total excursion of QRS in CR_1 was 1.290 mv., as compared to 1.449 mv. and 1.781 mv. in Leads CL_1 and CF_1, respectively. Similar data were obtained in Leads CR_2, CL_2, and CF_2. On the other hand, when the left foot electrode was used as reference point the deflections in leads from the left side of the precordium (CF_4, CF_5, and CF_6) were much smaller than in CR or CL leads from the same region. The difference in QRS excursion between CF and CR leads was least pronounced in cases in which there was a tendency toward left axis deviation and most marked when right axis deviation was present. The small R waves in V_F in group $\alpha \sim 30°$ (Table I) had relatively little influence upon the precordial records, but the large R waves in V_F in group $\alpha \sim 90°$ had an important effect. As shown in Table II, the average total QRS excursion in leads from the left midaxillary line were as follows: group $\alpha \sim 30°$, 2.020 mv. in CR_6, 1.463 mv. in CL_6, and 1.280 mv. in CF_6; group $\alpha \sim 90°$, 2.029 mv. in CR_6, 1.547 mv. in CL_6, and only 0.856 mv. in CF_6. On the average, the total QRS excursion in leads from the left side of the precordium in this last group was less than half as large in CF leads as in CR leads. These relations were reversed in leads from the right side of the precordium and near the base of the heart (CF_1, CF_2). Since the QRS deflections in V_L leads are usually intermediate in form between those in Lead V_R and in Lead V_F, CL leads are likewise intermediate between CR and CF leads as regards the form of QRS; this was not the case in group $\alpha \sim 30°$, in which slight left axis deviation was present. In this group V_L displayed large R waves which distorted the precordial electrocardiogram in CL leads in the same way as the large R waves of Lead V_F distorted these curves in group $\alpha \sim 90°$ (Table II).

When Wilson's central terminal (CT) was used as the reference point, precordial curves of essentially the same kind were obtained in all these groups ($\alpha \sim 30°$, $\alpha \sim 60°$, $\alpha \sim 90°$) (Table II). This indicates that a shift of the electrical axis has practically no influence on the precordial electrocardiogram when the latter is recorded in this way. This has been pointed out previously.[26] The individual deflections never reached their largest or smallest size, and the QRS group never

TABLE II

THE INITIAL VENTRICULAR DEFLECTION IN PRECORDIAL LEADS*
(IN TENTHS OF MILLIVOLT)

		RS				R				QS			
		CR	CL	CF	CT	CR	CL	CF	CT	CR	CL	CF	CT
V_1	$\alpha \sim 30°$	13.33	14.62	14.68	14.10	4.50	3.50	2.95	4.00	6.95	10.56	9.45	8.32
	$\alpha \sim 60°$	11.57	15.90	17.50	14.56	3.38	2.44	2.40	2.46	6.88	11.40	13.08	10.12
	$\alpha \sim 90°$	13.81	12.85	21.24	14.85	4.25	3.26	3.95	3.48	7.45	7.59	15.88	8.73
	Total	12.90	14.49	17.81	14.47	4.04	3.09	3.11	3.30	7.09	9.85	12.80	9.06
V_2	$\alpha \sim 30°$	18.83	18.88	19.60	18.10	9.32	4.52	5.02	5.62	8.60	13.93	12.31	10.92
	$\alpha \sim 60°$	16.49	20.10	20.60	18.35	4.86	4.18	3.76	4.14	10.34	14.10	15.36	12.73
	$\alpha \sim 90°$	21.08	19.85	28.65	23.85	5.94	4.86	5.54	5.50	12.86	12.60	19.38	16.08
	Total	18.80	19.61	22.25	20.10	6.71	4.49	4.77	5.09	10.53	13.54	15.68	13.24
V_3	$\alpha \sim 30°$	19.23	16.44	14.18	18.40	9.02	5.40	5.62	7.22	7.54	9.53	8.38	8.84
	$\alpha \sim 60°$	18.00	17.08	16.35	17.94	8.48	5.55	5.00	6.17	7.61	9.78	9.53	9.64
	$\alpha \sim 90°$	19.40	16.90	26.42	20.40	7.30	5.40	6.94	6.37	10.91	9.10	17.00	12.72
	Total	18.88	16.81	18.98	18.91	8.23	5.45	5.85	6.59	8.69	9.47	11.64	10.40
V_4	$\alpha \sim 30°$	22.48	18.08	17.85	17.00	15.00	8.98	10.72	12.78	4.28	4.68	4.63	4.28
	$\alpha \sim 60°$	20.95	18.48	16.70	17.85	13.35	10.12	9.46	10.70	5.50	5.98	6.35	5.12
	$\alpha \sim 90°$	25.54	20.45	18.62	20.04	17.08	14.12	6.97	12.61	6.00	3.82	9.28	5.74
	Total	22.10	19.10	17.72	18.30	15.14	11.07	9.05	12.03	5.26	4.83	6.75	5.05
V_5	$\alpha \sim 30°$	25.08	17.60	18.30	20.35	19.65	12.81	13.70	15.63	2.50	2.03	2.10	2.55
	$\alpha \sim 60°$	21.20	17.55	13.95	17.71	17.08	13.25	10.22	13.72	2.11	2.22	1.54	2.00
	$\alpha \sim 90°$	24.90	20.43	14.20	19.00	21.35	17.96	8.41	15.38	3.13	1.61	2.88	2.88
	Total	23.73	18.53	15.48	19.02	19.36	14.67	10.78	14.91	2.91	1.95	2.17	2.48
V_6	$\alpha \sim 30°$	20.20	14.63	12.80	16.30	15.53	10.13	9.17	12.30	2.23	2.07	1.33	1.85
	$\alpha \sim 60°$	18.42	13.20	10.58	14.81	15.12	11.28	7.32	11.10	1.25	1.00	1.07	1.01
	$\alpha \sim 90°$	22.24	18.78	8.50	15.82	17.85	15.31	4.12	11.94	2.46	1.35	1.43	1.43
	Total	20.29	15.47	10.63	15.64	12.83	12.23	6.87	11.78	1.98	1.47	1.28	1.43

*See footnote Table I.

showed its largest or smallest excursion in the central terminal leads, but always in leads in which the distant electrode was on one of the extremities. Considering the small number of samples, Table III shows a close agreement between the mean values of the sums of the heights of the deflections in CR, CL, and CF leads, divided by three, and the mean heights of the corresponding deflections in the leads obtained with the central terminal. Since the potential of the central terminal is necessarily at all times the mean potential of the three extremity electrodes, this result is predictable on theoretical grounds.

TABLE III

COMPARISON OF VALUES FOR INITIAL VENTRICULAR DEFLECTION IN PRECORDIAL LEADS WHEN A "CENTRAL TERMINAL" IS USED, WITH THE SUM OF THE VALUES FOR ELECTRODES ON LEFT ARM, RIGHT ARM, AND LEFT FOOT
(IN TENTHS OF MV.)

	RS		R		QS	
	CR + CL + CF / 3	CENTRAL TERMINAL	CR + CL + CF / 3	CENTRAL TERMINAL	CR + CL + CF / 3	CENTRAL TERMINAL
V_1	15.67	14.47	3.38	3.30	9.91	9.06
V_2	20.33	20.10	4.99	5.09	13.25	13.24
V_3	16.22	18.91	6.51	6.59	10.27	10.40
V_4	19.61	18.30	11.75	12.03	5.61	5.05
V_5	19.25	19.02	14.60	14.91	2.01	2.48
V_6	15.46	15.64	10.61	11.78	1.58	1.43

2. P waves.—The mean electrical axis of the normal auricular deflection is less variable than the mean electrical axis of the QRS complex, and no pronounced variations in the form of the P wave were encountered in the present series. This deflection was always upright in the standard limb leads, always inverted in V_R, and always upright in V_F. High, positive P waves occurred in all precordial leads when the indifferent electrode was on the right arm. Flat or inverted P waves were the rule in CF leads. When the central terminal or the left arm was the reference point, intermediate values for the P wave were obtained; in the present series of normal subjects the average height of the P deflection in Lead CR_6 was 0.149 mv., in Lead CL_6 it was 0.072 mv., in Lead CF_6, minus 0.004 mv., and, in Lead V_6 (central terminal), 0.076 mv. Isoelectric P waves were noted in one case when the central terminal was used as the reference point, in 2 cases when the left arm was so used, and in 8 cases when the left leg was used as the reference point. Inverted P waves were present only in CF leads, and occurred in these leads in 6 subjects. In only 6 instances (30 per cent) were positive P waves encountered in Lead CF_6.

3. T waves.—Uniformity in the position of the mean electrical axis of T is a striking characteristic of the normal electrocardiogram. Slight shifts to the right, which are often noted in the mean axis of QRS, do not occur in the axis of T in normal subjects. Inversion of the T wave in Lead I is, in other words, distinctly abnormal. Moderate shifts to the left are occasionally encountered (inverted T waves in Lead III). The normal T-wave pattern in the unipolar limb leads (extremity potentials) is similar to the normal pattern of the auricular deflection; the T wave is uniformly downward in V_R and uniformly upright in V_F (Table I). Large positive T waves are seen in CR leads, whereas flat T waves are the rule in CF leads. The height of the T wave in CL leads depends on the magnitude and direction of T in Lead V_L. Since T in this lead is usually upright, the T wave in CL leads tends to resemble that of the CF leads. Whatever connection was used, the T waves were upright in most of the precordial leads which were taken. Inverted T waves were present eight times in Lead CF_1 and seven times in Lead CL_1, but inverted T waves were never seen in CR_1. Diphasic T waves were present three times in Leads CF_1 and CL_1, and once in Lead V_1 (central terminal). In normal subjects with a tendency toward left axis deviation of the QRS complex, the mean axis of T also tends to shift slightly to the left. The largest T waves in Lead V_L occurred in the group $\alpha \sim 30°$ (Table I), whereas the two other groups ($\alpha \sim 60°$, $\alpha \sim 90°$) showed high T waves only in Lead V_F.

DISCUSSION

Although the influence of the position of the reference electrode upon the precordial electrocardiogram in normal subjects is rarely very striking, it is significant enough to warrant careful consideration.

That the potential variations of the extremity which is used as the reference point are responsible for distortion of the precordial electrocardiogram is to be expected. Their influence can be demonstrated by recording them directly by means of unipolar limb leads (extremity potentials). The distortion is most pronounced when the extremity used as the reference point is the one which displays the largest potential variations. The extremity which is least desirable as a reference point varies from subject to subject with the average direction of the electromotive force produced by the heart. Unipolar leads from the left arm show large deflections when left axis deviation is present ($\alpha \sim 30°$). The potential variations of the left leg are large when the electrical axis is nearly vertical ($\alpha \sim 90°$). The potential variations of the right arm are much more uniform in normal subjects than those of the other extremities. In many respects they resemble those which have been recorded from the ventricular cavities in animal experiments. They are not greatly influenced by axis deviation unless it is extreme. Consequently, if the right arm is used as the reference point in recording precordial leads from normal subjects, the results are much more uniform than when the left arm or the left leg is employed. Since the largest deflections are downward when the exploring electrode is placed on the right arm (Lead V_R), the potential variations of this extremity are of a kind which tends to produce upward deflections when this electrode is shifted to the chest and the indifferent electrode is placed on the right arm. The uniformly negative potential of the right arm during the greater part of the QRS interval must increase the height of the deflection in CR leads, which represent positivity of the precordium. The R waves of these leads are, for this reason, unusually large as compared to the R waves of other chest leads. This is shown in Table II; it has been stressed by many recent investigators.[2, 5, 6, 14, 16] The fact was known to Einthoven and de Lint[27] as early as 1900, i.e., before the introduction of the string galvanometer! However, it has not been sufficiently emphasized that the increased size of R under these circumstances is the result of a summation of the effects of the heart upon the potentials of two electrodes (precordial and right arm). The argument that CR leads are best because they yield the largest deflections is not sound, for it can be clearly demonstrated that the increased height of the deflections is caused by the large negative potentials of the right arm electrode. For similar reasons it cannot be expected that the left leg, which is so commonly used as reference point, gives more accurate results than any other proposed connection. The high R waves in V_F (Table I) will produce deep S waves and subtract from R waves in CF leads for the same reason that deep S deflections in Lead V_R tend to produce high R waves and diminish S waves in CR leads. Here again we are dealing with a summation of effects, with a distortion of the precordial electrocardiogram. Table II indicates that deflections in apical leads are usually smaller in CF than in CR, CL, or central terminal leads. The potential variations

of the apical region and those of the left leg are similar when the electrical axis is in an approximately vertical position, as is commonly the case in normal subjects, relative to the potential variations of the left ventricular surface. The combination of apex—left leg is therefore really an "unfavorable lead" in Waller's sense. The popular IV F lead belongs to this group.

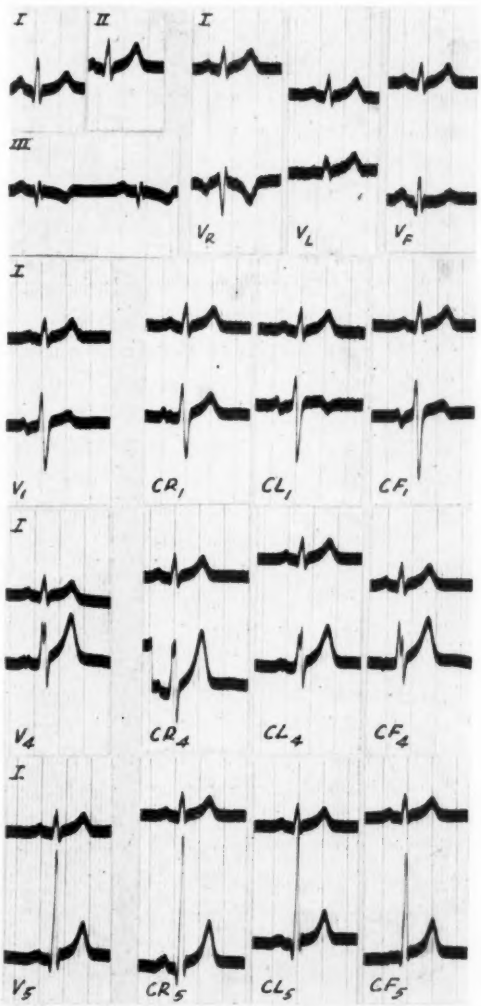

Fig. 6.—To conserve space, only 3 of the 6 precordial leads are reproduced (V_1, V_4, V_5). J. C., 35 years old. Draftee. Tendency to left axis deviation.

Top row: standard leads (N/sens.), extremity potentials (2N/sens.).

2nd row: leads from 4th intercostal space at right sternal border. Note inverted *T* in *CL* (positive *T* in V_L); *P* waves positive in *CR*, biphasic in *CL*, inverted in *CF* (negative in V_R, isoelectric in V_L, positive in V_F).

3rd row: leads from 5th intercostal space in left midclavicular line. Note split top of *R* in all leads. Second spike higher than first in *CL* (large *R* wave in V_L), first spike higher than second in *CF* (large *Q* wave in V_F). These differences remained constant and were not influenced by respiration.

4th row: leads from 6th intercostal space in left anterior axillary line. Relative similarity of pattern except for *P* waves and slurring of ascending limb of *R* in *CF*, caused by large *Q* waves in V_F.

Lead I simultaneously, chest leads at N/sens.

Our discussion has been confined to general gross effects, but the influence of the reference electrode may make itself felt even in details of the QRS group. A large Q wave in Lead V_F will add to the ascending limb of R in precordial leads and subtract from precordial Q waves if the left leg is used as reference point (Fig. 6); it may even cause a slight notch in the R wave. Large S waves in V_F will diminish the S waves in CF leads, etc. By recording the extremity potential variations the influence of the reference electrode can nearly always be predicted in considerable detail.

The same rules apply, of course, to the configuration of the auricular deflection. A strongly negative P wave was always present in Lead V_R. When the polarity is reversed and the exploring electrode on the arm is replaced by the reference electrode, the effect is to increase the size of the auricular deflection in precordial leads. This explains why CR leads yield such "good results" in the case of the auricular deflections. For similar reasons CF leads result in small, positive, isoelectric, or negative auricular deflections. Since P waves are largest in leads from the right side of the precordium and almost disappear when the exploring electrode is shifted toward the apex,[24, 26] CF leads have a strong tendency to display inverted P waves in leads from the left side of the precordium. The negative potentials of the leg Lead V_F is not opposed by a significantly positive precordial potential. Whether the P waves are positive, isoelectric, or negative in CL leads depends again on the direction and magnitude of the P deflection in Lead V_L. Such leads resemble CR leads if P is negative in Lead V_L, and CF leads when it is upright in V_L.

The influence of the reference electrode on the T wave of the normal precordial electrocardiogram is rarely very conspicuous because a large positive T wave is an essential feature of the precordial electrocardiogram of normal adult subjects. Slight additions to, or subtractions from, this wave (distortions from the distant electrode) are of little significance. The position of the reference electrode is important in leads from the extreme right side of the precordium, in which the T waves are occasionally flat or inverted. The large positive T waves regularly encountered in Lead V_F cause inversion of the precordial T waves in Lead CF_1 in almost half the cases. They are also responsible for relatively flat T waves in Leads CF_5 and CF_6. It is conceivable that an unusually large T wave in V_F may cause a diphasic or even an inverted T wave in Leads CF_5 and CF_6 in normal subjects. Such an extreme case was not observed in our group, but it may well explain inversion of T in Lead IV F in a normal person, which was reported by Sodeman.[28]

The conflicting reports concerning the relative merits of one reference electrode point as compared to others resolve into a question of what type of patients are to be examined. Those with a tendency to left axis deviation will show gross distortion of the precordial electrocardiogram in CL leads; those with right axis deviation will

show more distortion in CF leads. The last is true also of those without axis deviation, as has been pointed out in a previous paragraph, and has been stressed by Deeds and Barnes.[2]

It is, of course, not feasible to ascertain the direction and amplitude of the potential variations of each of the extremities in every individual patient, and then chose the best connection. With the introduction of the central terminal into electrocardiography this has become unnecessary. The central terminal shows little if any variations of potential, and the results obtained with it are relatively uniform. It is almost as simple to use as any other method, and the materials necessary for its construction can be easily obtained. Whether or not the potential of the central terminal is entirely unaffected by the heart beat is of little practical importance as long as its potential variations are negligibly small or markedly smaller and much more uniform than those of the extremities. That this is the case seems certain from the present study, as well as from theoretical considerations[25] and the experiments of Eckey and Fröhlich.[19] The distortion caused by the reference electrode may in exceptional cases be helpful, and in such cases an electrode on one limb alone may be preferable to the central terminal. Chest leads are sometimes employed for better demonstration of the auricular deflections when these are masked or hardly detectable in the standard limb leads. For this purpose the right arm may serve better as the reference point than any other extremity or the central terminal.

When the purpose is to ascertain with greatest accuracy the form of the potential variation of the precordium, the central terminal should be used as the reference point.

SUMMARY

1. Standard limb leads, unipolar limb leads (extremity potentials), unipolar precordial leads, and precordial leads of the CR, CL, and CF types were taken in a series of normal subjects. Analysis of the curves thus obtained justifies the following conclusions:

2. The position of the reference electrode has a considerable effect upon the size and form of the normal precordial electrocardiogram.

3. The potential variations of the left arm in CL leads and the influence of the potential variation of the left leg in CF leads vary with the position of the mean electrical axis of P, QRS, and T. The distortion which occurs in CR leads is not appreciably less than that in CL and CF leads, but is much more uniform in magnitude and in duration when the electrical axes of P, QRS, and T are in a relatively normal position.

4. When a central terminal is employed, the distortion introduced by the reference electrode is eliminated or reduced to a minimum.

The author wishes to thank Dr. F. N. Wilson for his many suggestions in the preparation of this paper.

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QUINIDINE, "PURE QUINIDINE," AND HYDROQUINIDINE

I. Toxicity

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COMMERCIAL quinidine is composed of about 80 per cent "pure quinidine" and 20 per cent hydroquinidine. The well-known effect of quinidine in cases of auricular fibrillation is, according to Van Dongen and Sanches,[1, 2] due to hydroquinidine. These investigators have shown that hydroquinidine lengthens the refractory period and increases the auricular and auriculoventricular conduction time, and that "pure quinidine" does not have these effects, which means that it is more or less inert.

We have been conducting a series of experiments on dogs to ascertain the comparative toxic and pharmacologic effects of quinidine, hydroquinidine, and "pure quinidine." Through the cooperation of Merck and Company, we were furnished with these preparations. However, the purest "pure quinidine" that we could obtain contained about 8 per cent hydroquinidine.

Our first study was concerned with comparing the toxic effects of these drugs on dogs. The drugs were given intravenously in sublethal doses.

Table I

General Average Value of the Efect of the Three Quinidines on Blood Pressure, Pulse Rate and Respiratory Rate

Time	"Pure Quinidine"			Commercial Quinidine			Hydroquinidine		
	B.P.	Pulse	Respir.	B.P.	Pulse	Respir.	B.P.	Pulse	Respir.
Normal	142	154	13	136	164	13	151	152	18
End of Q* injection	38(13)	99	15	52(11)	100	14	94(7)	151	19
5 min. after	34(5)	105	19				127(3)	132	17
15 min. after	40(4)	111	15	60(7)	93	13	114(5)	126	18
30 min. after	66(3)	129	17	68(5)	120	14			
1 hr. after	96(2)	167	20	94(4)	159	15	128(6)	130	22
2 hr. after	112(4)	166	13	112(5)	139	18	147(5)	192	22
3 hr. after	115(4)	138	20	132(7)	115	18	155(2)	204	31
	Death rate, 46.1%			Death rate, 18.2%			Death rate, 0.0%		

The above figures are simply tabulated to give a general view of the effect of the three quinidines on blood pressure, pulse, and respiration.

Because of experimental conditions, the exact time interval could not always be recorded.

The figures in parentheses indicate the number of animals that have been taken into account for the specific time stated.

*Q = Quinidine.

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This work was carried out with the aid of a grant from the Graduate School, University of Minnesota.

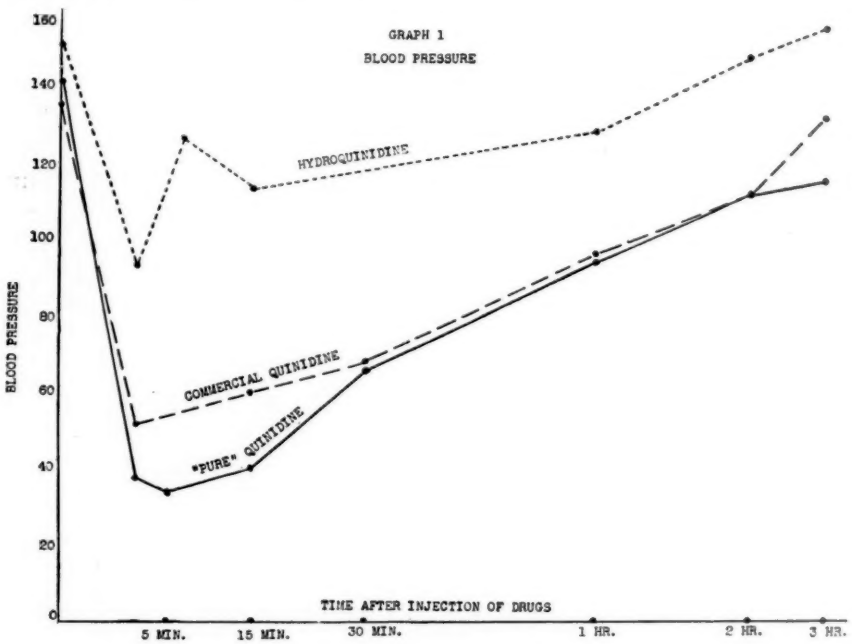
Assistance in the preparation of these materials was furnished by the personnel of Works Progress Administration, official project No. 665-71-3-69.

Received for publication Feb. 25, 1942.

In previous studies we found that 45 mg. per kilo of quinidine was a sublethal dose.[3] Comparable doses of hydroquinidine were used; the amount was estimated on the basis of the fact that this drug composes about 20 per cent of the commercial product. A summary of these experiments is shown in Table I.

COMMERCIAL QUINIDINE

Eleven experiments were carried out with this drug. A sublethal dose of 45 mg. per kilo of quinidine was used. There were two deaths, a mortality rate of 18.2 per cent.



HYDROQUINIDINE

Seven experiments were done in this study. In only one dog did we use the actual minimal lethal dose, 9 mg. per kilo, which is 20 per cent of the lethal dose of quinidine. We increased the amounts of hydroquinidine to 20 mg. per kilo. This amount, theoretically, is twice the sublethal dose. There were no deaths in this series of experiments. As the dose of hydroquinidine was increased, convulsions tended to appear about one hour after the administration of the drug. These often lasted for an hour or more, and continued even after the animal recovered from the anesthesia.

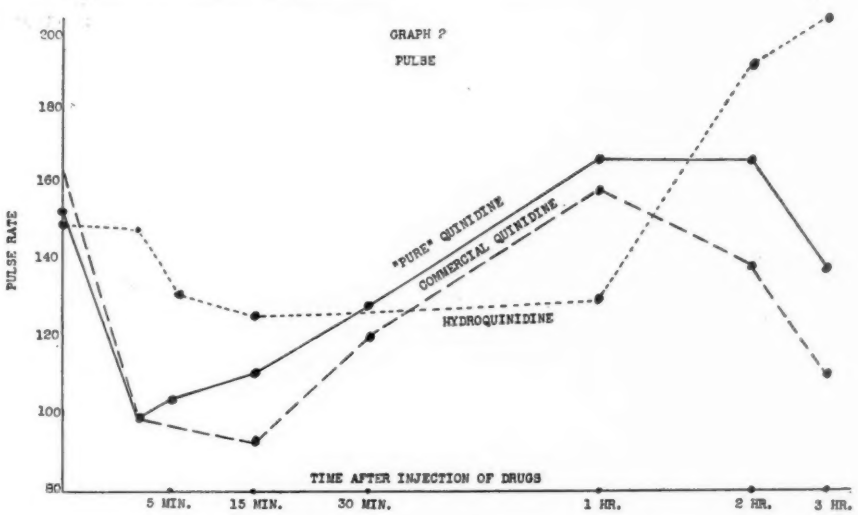
"PURE QUINIDINE"

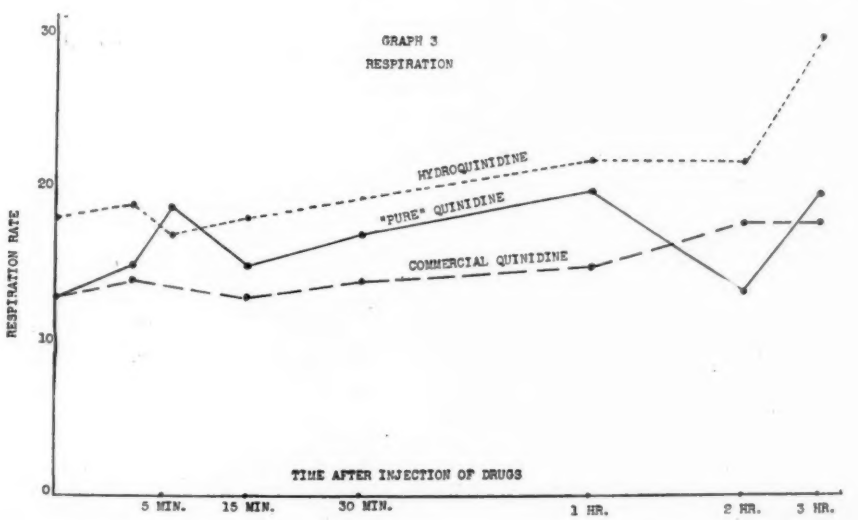
Sixteen experiments were carried out with this drug. Three studies were made on one dog, using very small doses. Thirteen dogs were given

sublethal doses, 45 mg. per kilo, and six dogs died. In the thirteen experiments in which sublethal doses were used, there was a mortality rate of 46.1 per cent.

BLOOD PRESSURE

The greatest fall in blood pressure followed the administration of "pure quinidine" (Graph 1). The blood pressure did not immediately recover after the initial fall, as it did after giving the other two preparations. The blood pressure after the injection showed a tendency to remain for a longer time at a low level, and often would fall even a little more before tending to rise again. "Pure quinidine" appeared to be the most potent vascular depressant.





The effect of regular quinidine is well known. Usually there is an immediate fall in blood pressure after its administration, after which there is a prompt tendency for the blood pressure to rise again.

Hydroquinidine caused the least fall in blood pressure. The fall after its administration was about one-half that which followed the administration of the other two drugs. The recovery, however, was much more rapid. After a period of about two hours the blood pressure rose above the level at which it stood before the drug had been given.

PULSE RATE

The pulse rate is slowed more by quinidine and "pure quinidine" than by hydroquinidine (Graph 2). The rate remains slower for about 10 minutes longer after giving quinidine than after the administration of "pure quinidine." The initial rate is reached before one hour after giving the drugs. Hydroquinidine is the least depressing on the pulse rate. The effect is very slight. In about one hour the pulse rate begins to increase, and soon reaches a higher level than was present before the administration of the drug.

RESPIRATION

There was no depressing effect on respiration as a result of administering "pure quinidine," regular quinidine, or hydroquinidine (Graph 3). There appeared to be a slight increase in respiratory rate after "pure quinidine" and hydroquinidine.

SUMMARY

1. Quinidine is composed of about 20 per cent hydroquinidine and 80 per cent "pure quinidine."

2. "Pure quinidine" is a marked cardiovascular depressant. It is much more toxic than quinidine in doses equivalent to sublethal doses of quinidine.

3. The mortality rate which resulted from giving quinidine in sublethal doses was 18.2 per cent.

4. The mortality rate as a result of giving "pure quinidine" in sublethal doses was 46.1 per cent.

5. No mortality resulted from using equivalent sublethal and larger doses of hydroquinidine.

6. Hydroquinidine is a very slight cardiovascular depressant.

7. The hydroquinidine fraction of quinidine appears to counteract to a great degree the cardiovascular depressant action of the "pure quinidine" fraction.

Eight patients with chronic auricular fibrillation were treated with hydroquinidine. In not one case was normal rhythm restored. This study will be reported at some future date.

The writer wishes to express his sincere thanks to Dr. A. D. Hirschfelder for much valuable advice and help in carrying out this study, and to George Tamcales for technical assistance.

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Clinical Reports

ANEURYSM OF ONE OF THE SINUSES OF VALSALVA CAUSED BY A CONGENITAL LESION

CASE REPORT

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ANEURYSM of one of the sinuses of Valsalva may be part of a more diffuse aneurysm involving the proximal portion of the aortic arch, but may also occur as an isolated entity as a result of syphilis, arteriosclerosis, ulcerative endocarditis, or a congenital lesion. Micks[1] states that twelve, including his case, have been of congenital origin. Usually the right aortic sinus alone is involved. Four instances have been reported in which aneurysms were present in the three sinuses.

There appears to be some confusion in regard to the nomenclature of the aortic sinuses, but for clinical purposes a division into right, left, and posterior sinuses is most acceptable. The right sinus is marked by the fact that the right coronary artery arises from it; the left coronary originates in the left sinus. The posterior sinus may be designated as the "noncoronary" sinus. The sinuses are intracardiac in their anatomic relations. The signs of aneurysm are caused partly by involvement of the aortic ring and partly by secondary pressure on the surrounding cardiac structures. The location of the sinuses determines the direction in which the aneurysm will extend. The right sinus is in juxtaposition to the right auricle and ventricle. The left sinus lies external to the left ventricle and internal to the pericardial sac. Enlargement of an aneurysm of the left sinus may reveal itself on the external topography of the heart because of its relation to the pericardial sac, which is usually at a point to the left of the pulmonary artery; the posterior sinus is located anterior to the right and left auricles.

Since the aneurysms are almost invariably intracardiac, they are often associated with unusual murmurs and thrills. The proximity of the right sinus to the membranous portion of the septum occasionally produces conduction disturbances. Compression by the contiguous heart muscle and lack of freedom of expansion usually prevent the aneurysms from growing very large, but they frequently attain the size of a hen's egg. Since the coronary orifices arise in proximity to the sinuses, they may become aneurysmal by contiguity. Disturbance of the function of the aortic valve is not uncommon. Sinus aneurysms may rupture into the

Received for publication Feb. 1, 1941.

pericardium, the vena cava, the pulmonary artery, or one of the heart cavities. Death may ensue rapidly with rupture into the pericardium, but when rupture occurs into a heart cavity, the pulmonary artery, or one of the large venous trunks, death does not always occur immediately, and sudden changes in the palpatory and auscultatory signs may be noted. Such signs and symptoms of marked change in the circulatory mechanics develop abruptly and are plainly evident.

In the case reported in this paper, the aneurysm apparently arose at the site of a congenital defect in the aortic ring, and originated in the right sinus. The posterior sinus was rudimentary. Aneurysms which project from the right sinus tend to bulge through the septum between the ventricles, and extend anteriorly into the conus of the right ventricle 1 or 2 cm. below the pulmonary ring. Involvement more to the right will produce bulging into the right ventricle in the region of the tricuspid valve commissure on the anterior or right septal surface, and may cause relative insufficiency or stenosis of the valve. Aneurysms may rupture into the right auricle or ventricle, and, because of encroachment on the interventricular septum, may cause intraventricular conduction defects.

CASE REPORT

A. L. H., a man, aged 20, a student, was admitted to St. Mary's Hospital February 18, 1939, and died February 26, 1939. He was under the care of Dr. F. W. Spicer, and was seen in consultation on February 23, 1939, by Drs. F. W. Spicer and F. J. Hirschboeck.

On admission to the hospital the patient complained of extreme shortness of breath, pain in the chest, vomiting, and disorientation. The history was obtained from the mother, who stated that the patient had had a somewhat similar experience about a month before, when he suddenly began to vomit and had severe pain in his chest, with shortness of breath. These symptoms continued for about three days, and then the patient appeared to improve for about three weeks.

Past History.—The patient had always been very active, and participated in athletics, including football. There was no history of rheumatic fever or any previous suggestion of congenital heart disease, and the patient had always been well except for the diseases of childhood, which were not associated with any complications.

Physical Examination.—The patient was a rather robust white man, 20 years of age; he weighed about 160 pounds.

Examination of the eyes, ears, nose, and throat was negative. The pupils were normal and equal, and reacted to light and in accommodation. It was noted that there was prominent pulsation in the carotid vessels. The veins were not distended in the neck, but were visible in the upper portion of the chest. A pulsation was also observed in the epigastrium. The heart was enlarged diffusely. Careful measurements were lacking. There was a marked systolic thrill over the apex, and a harsh systolic murmur was audible at the lower end of the sternum and in the epigastrium. On admission to the hospital his blood pressure was 300/0. The heart rate was 140. There was no evidence of any abnormality of the lungs. The liver dullness was about two fingerbreadths below the right costal margin. Over the peripheral vessels a pistol-shot sound was audible.

Laboratory Data.—On two occasions the hemoglobin was 91 and 94 per cent, and the erythrocyte count, 4,810,000 and 4,700,000, respectively. The leucocyte count on February 19 was 11,400, and, on February 23, 18,800. A differential

leucocyte count showed 77 polymorphonuclear cells, and 11 small and 12 large lymphocytes. The blood urea nitrogen was 18 mg. per cent, and the creatinin, 2 mg. per cent. Blood cultures on two occasions were negative, and remained negative after the death of the patient. The urine was normal except for a trace of albumin; the specific gravity was 1.024 to 1.030.

A roentgenogram of the chest, taken in bed, showed what seemed to be enlargement of the heart to the right and left, but more particularly to the right. An electrocardiogram showed right axis deviation, low voltage in all the leads, inversion of T_1, an isoelectric T_2 and T_3, elevation of ST_1, and slurring of the QRS in all leads.

The temperature fluctuated from normal to 103° F.

A tentative diagnosis of subacute bacterial endocarditis was made.

On February 23 it was noted that the heartbeat was very rapid (130) and tumultuous. The murmurs were harsh and seemed to be chiefly systolic; they were at the lower end of the sternum and in the epigastrium, as previously observed. The blood pressure at that time was 200/0, and, although the rapidity of the heart made it difficult to interpret the murmurs at the base, it was thought that a diastolic murmur was heard. The next day the heartbeat was less rapid, and a diastolic murmur could be heard plainly at the left border of the sternum and in the aortic area. The diagnosis was aortic insufficiency and tricuspid insufficiency, caused by endocarditis of undetermined origin. On February 26 the patient became rapidly weaker and died.

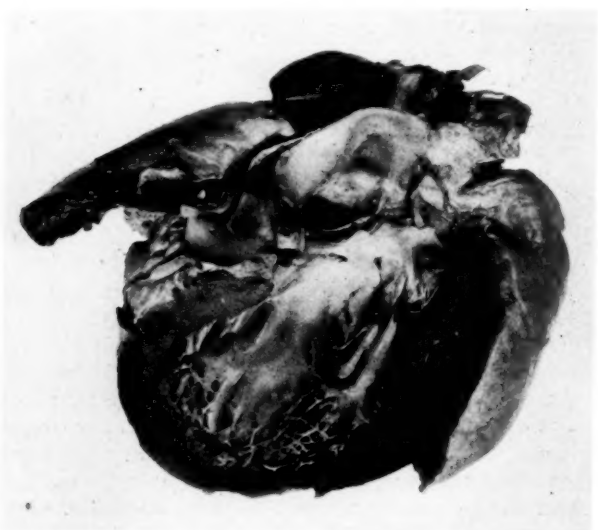

Fig. 1.—View of the left ventricle and aortic opening. Opening of the aneurysm is plainly seen in the right aortic sinus. Its relative size as compared to the rudimentary posterior sinus is manifest.

Autopsy.—On opening the abdominal cavity the peritoneal cavity was found to contain about 800 c.c. of clear, straw-colored fluid. The liver reached the costal margin in the right midclavicular line. The left pleural cavity contained 600 c.c. of clear, straw-colored fluid, and the right pleural cavity, 300 c.c. There were no pleural adhesions. The pericardium contained 250 c.c. of clear, straw-colored fluid. The heart weighed 445 Gm., the liver, 2,000 Gm., the spleen, 220 Gm., and the kidneys, 350 Gm.

The heart was about one and one-half times the size of the deceased's fist, and the cavities were dilated, mainly on the right side. The cavities of the heart con-

tained fluid blood. There were numerous small hemorrhages under the epicardium, mainly on the right side and along the sinus venosus. The pulmonary valve was normal in appearance. The cusps of the aortic valve were quite unequal; the left and the right cusps were larger than usual, and the posterior cusp was undeveloped and rudimentary. The openings of the left and right coronary arteries were in the normal position. The right aortic sinus was deeper than usual, and, in the deepest portion of the sinus, below the opening of the right coronary artery, the wall of the aorta was the seat of a round defect, measuring about 1 cm. in diameter, through which blood had passed into the right side of the heart. The point of emergence of the aneurysmal cavity, as seen from the inside of the right heart, was sac-like; it measured about 1.2 cm. in diameter, and lay prominently between two of the tricuspid leaflets. The sac-like structure was formed by a thin layer of connective tissue, and at its apex there was an irregular tear about 1 cm. in length; rupture had apparently occurred recently. There were no fresh or old endocardial deposits on the valves or walls of the heart. The mitral valve admitted three fingers and appeared normal.

Fig. 2.—Exposed right side of the heart. The opening of the aneurysm at the tricuspid orifice is shown. Its position and the transmission of the jet toward the cavity of the right ventricle are also noted.

The tricuspid valve admitted four fingers; two of the leaflets were held apart by the encroachment of the aneurysm. The foramen ovale was closed. The interventricular septum was normal. The coronary arteries were normal in appearance. The myocardium was normal in appearance. The wall of the ventricles was moderately hypertrophied, mainly on the right side.

Examination of the lungs showed some punctate hemorrhages on the visceral pleura. The left lung was the seat of marked and diffuse congestion, particularly in the posterior portion of the lower lobe. The right lung was similarly but less

affected. The pulmonary artery appeared to be normal. The spleen had a slightly increased consistency, but was otherwise normal. The kidneys were normal. The liver showed moderate central passive congestion; the periphery of the lobules was somewhat yellowish.

The post-mortem diagnosis was malformation of the aortic valve, with aneurysm of the right aortic sinus which extended through the ventricular wall and emerged as a sac-like projection into the right auricle and encroached upon the tricuspid orifice; rupture of the aneurysm, with formation of a shunt between the aorta and right ventricle: congestion, Grade III, and edema, Grade II, of the lungs; central passive congestion of the liver; bilateral hydrothorax; ascites.

Microscopic examination of the heart showed slight fragmentation, but nothing else abnormal.

This case was interesting because a congenital anomaly of the aortic ring was found, with a rudimentary posterior cusp. There was an aneurysm which arose at the base of the right aortic sinus and extended through the wall of the ventricle into the right auricle; it emerged at the tricuspid orifice, and ruptured in the direction of the right ventricle. Of interest clinically was the extremely high pulse pressure; on one occasion the blood pressure measured 300/0. This is explained in part by the relative aortic insufficiency caused by the proximity of the aneurysm to the aortic ring, and in part by the development of an arteriovenous shunt from the aortic ring into the right side of the heart. These two factors evidently combined to cause the unusual blood pressure. Clinically, it was possible to detect the functional disturbance in the valve, but the anatomic cause was not recognized.

It would seem that the aneurysm was caused by a congenital anomaly and weakness of the aortic valve ring.

NOTE.—The right axis deviation in the electrocardiogram, in view of the extreme hypertension, was thought unusual. William B. Porter, in the AMERICAN HEART JOURNAL, Vol. 23, page 468, describes similar occurrences, with rupture of the aortic aneurysm into the pulmonary artery. The analogy between the instances described by Porter and this case, in which aortic aneurysm ruptured into the right side of the heart, is evident.

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QUINIDINE AND POTASSIUM IN THE TREATMENT OF REFRACTORY PAROXYSMAL VENTRICULAR TACHYCARDIA

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PAROXYSMAL ventricular tachycardia is a rare but highly important cardiac disorder which demands prompt, energetic treatment. Unless this abnormal rhythm is stopped, congestive failure eventually supervenes, and leads to a fatal outcome.

Quinidine is by far the most reliable drug in the treatment of paroxysmal ventricular tachycardia. Levine[1] states that atropine may be used as an adjunct to quinidine therapy if the latter alone is not effective. Sampson and Anderson[2] studied the effects of potassium salts alone in a group of fifty-eight patients with cardiac arrhythmias. Only one of these was a case of paroxysmal ventricular tachycardia. This patient was a thirty-year-old man with premature arteriosclerosis. He was observed during four attacks of paroxysmal ventricular tachycardia which lasted from sixteen hours to five days. Each attack ceased within one hour after the oral administration of a total of two to ten grams of either potassium chloride or potassium acetate.

Since there are very few clinical observations on the use of potassium in the treatment of ventricular tachycardia, we wish to report a gratifying experience with this drug in a patient whose tachycardia was highly refractory to treatment with quinidine and other drugs, but stopped promptly when, in addition, potassium chloride was given orally.

CASE REPORT

A seventy-three-year-old man was admitted to the Fifth Medical Service of the Boston City Hospital on August 23, 1940, with the chief complaint of precordial oppression, palpitation, and wheezing dyspnea of sudden onset twenty-four hours previously. A similar attack, associated with prolonged, severe pain in the anterior portion of the chest, had occurred in June, 1940. Later information from the family physician disclosed that the earlier attack had been caused by coronary occlusion, as proved by an electrocardiogram taken June 31, 1940.

On admission, physical examination revealed a well-nourished, elderly white man with orthopnea and Cheyne-Stokes respiration, but no cyanosis. His heart was considerably enlarged to the left and right. The heart rate was estimated at 208 beats per minute. The heart sounds were distant and of uniform quality. No murmurs or friction rubs were audible. No appreciable effect on the rhythm could be produced by carotid or ocular pressure. The blood pressure was 100/75. The neck veins were distended and the liver was palpated two fingerbreadths below the right costal margin. Moist râles were heard at the bases of both lungs. No peripheral edema was demonstrable.

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Received for publication Feb. 26, 1941.

August 23.—Without the help of the electrocardiogram, it seemed that the cardiac abnormalities on admission were suggestive of paroxysmal auricular tachycardia and congestive heart failure. Therefore, moderately rapid digitalization was started. The only effect was a decrease in the heart rate from 208 to 176 beats per minute.

August 24.—The electrocardiogram showed paroxysmal ventricular tachycardia. Thereupon, digitalis was discontinued and quinidine therapy was started. A total of thirty-three grains of quinidine was given orally in divided doses throughout the remainder of the day. The only effect was a further decrease in the ventricular rate from 176 to 160 beats per minute.

August 25.—Twenty-four grains of quinidine were given orally in divided doses without effect on the ventricular rhythm.

August 26.—The dose of quinidine was increased to forty-eight grains daily (six grains every three hours) and maintained at this level. No change in the ventricular rate was observed.

August 27.—Another electrocardiogram showed persistence of the ventricular tachycardia. The signs of congestive failure appeared to be increasing.

August 28.—Twenty c.c. of a ten per cent solution of magnesium sulfate were injected slowly by vein without demonstrable effect. The electrocardiogram was recorded frequently during this injection.

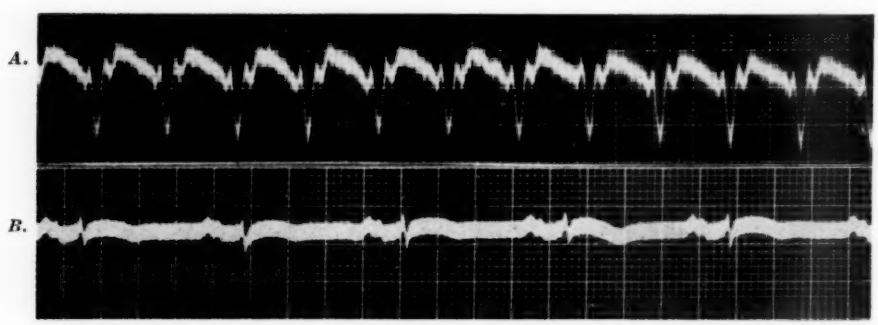

Fig. 1.—Electrocardiograms (Lead II) showing: *A*, Ventricular tachycardia before use of potassium. *B*, Normal sinus rhythm after the addition of potassium to the quinidine therapy.

August 29.—Five grains of quinine dihydrochloride were injected intravenously, but no change in the ventricular rate was noted.

August 30.—Five grains of quinine dihydrochloride were given intravenously without effect. One-sixtieth of a grain of atropine sulfate was given intravenously, with electrocardiographic control, without demonstrable change in the ventricular rate and rhythm.

August 31.—Potassium chloride was added to the quinidine therapy in a dose of fifteen grains every four hours. Shortly after the third dose of potassium chloride, the ventricular rate dropped abruptly from 152 to 80 beats per minute.

September 1.—Potassium chloride was discontinued, and the dose of quinidine was reduced to twenty-four grains daily.

September 3.—An electrocardiogram showed normal sinus rhythm and T waves which were more nearly normal than those in the record of June 31.

After the return of the ventricular rate to normal, the signs of congestive failure rapidly disappeared. The patient was discharged, fully recovered, October 31, 1940, on a maintenance dose of 18 grains of quinidine daily.

DISCUSSION

There is considerable experimental evidence to indicate that potassium has striking effects on myocardial function. Sollmann,[3] in 1926, working with turtle hearts, demonstrated that potassium in small concentrations exerts a depressant action which affects rhythmicity much more than contractility. Wiggers[4, 5] and Hoff and Nahum,[6, 7] working with mammalian hearts, have shown that potassium salts at certain optimal concentrations depress conduction, either locally at the site of direct surface application, or, when given intravenously, in more widespread portions of the conducting system and myocardium. Winkler, Hoff, and Smith[8] demonstrated striking electrocardiographic changes in dogs after the intravenous injection of isotonic potassium chloride solution. They found that, as the concentration of the serum potassium increased, the following changes occurred: alterations of the T wave; depression of the S-T segments; intraventricular block; disappearance of the P waves; and, finally, cardiac arrest. A comparable study in man, made by Harris and Levin,[9] showed that an increase of potassium in the blood stream caused:

A. A decrease in the heart rate by virtue of a lengthened diastolic interval (T-P); *B.* occasional diminution of the height of the P and R waves; and *C.* occasional, slight prolongation of the P-R and Q-T intervals.

More recently, Thomson,[10] who studied the effects of the oral ingestion of potassium salts on the human electrocardiogram, demonstrated changes in the T waves in fifteen cases and impairment of conduction in two cases out of a total of twenty-four cases. This author is of the opinion that the effect of vagal stimulation and acetylcholine on the heart may be mediated through the action of the potassium ion on the myocardium. Furthermore, Camp (quoted by Thomson[10]) has shown that, in dogs, potassium definitely potentiates the vagus action of digitalis.

Not much clinical use has been made of these cardiac effects of potassium. Sampson and Anderson,[2] as previously mentioned, were able to abolish extrasystoles in many of their cases, and ventricular tachycardia in one case, by giving potassium salts by mouth.

On the other hand, quinidine has been applied generally and successfully in the treatment of certain cardiac arrhythmias. But it is not unusual to find that a frequently reliable remedy may, in an individual case, prove entirely ineffective. The ventricular tachycardia described in this report proved to be refractory to treatment with large doses of quinidine. It further failed to respond to the parenteral administration of certain other drugs, namely, magnesium sulphate, quinine dihydrochloride, and atropine sulphate. Finally, after nine days of continuous ventricular tachycardia despite quinidine therapy, an abrupt change to normal rhythm occurred after the oral ingestion of three grams of potassium chloride.

SUMMARY AND CONCLUSIONS

1. Quinidine alone may be ineffective in the treatment of ventricular tachycardia.

2. Certain adjuncts to quinidine therapy, such as magnesium sulphate, quinine dihydrochloride, and atropine sulphate, may also prove ineffective.

3. Under such conditions, we recommend giving potassium salts in addition to the quinidine therapy. One or two grams of potassium chloride or potassium acetate may be given every two to four hours until a favorable response is obtained.

4. We believe that the action of potassium in our case was specific and not fortuitous for these reasons:

(a) Potassium depresses the conductivity and excitability of the myocardium.

(b) Potassium potentiates digitalis and quinidine.

(c) Potassium alone can abolish extrasystoles and paroxysmal ventricular tachycardia in man.

(d) Lastly, the long duration of the tachycardia, the lack of response to quinidine and other adjuncts, and the prompt response when potassium was added seem to support a cause-and-effect relationship.

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AN UNUSUAL TOXIC MANIFESTATION OF THE ORAL USE OF QUINIDINE SULFATE

Report of a Case

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THE toxic manifestations of quinidine and quinine are numerous and well known. Immediate febrile reactions as a result of the administration of quinidine sulfate have not been reported. The case here described illustrates this unusual manifestation of sensitivity to the drug.

REPORT OF CASE

The patient, H. B., a 65-year-old married tailor, was admitted to the Beth Israel Hospital October 10, 1940, because of the sudden onset of shortness of breath. His health had been excellent until four months prior to entry, when he experienced extreme generalized weakness and profuse perspiration while at work. Two weeks later, he developed severe pain in the chest, and a diagnosis of coronary thrombosis with myocardial infarction was made at another hospital. Recurrent substernal pain necessitated readmission to the same institution, but there was no confirmatory evidence of another infarction.

Physical examination disclosed a fairly well-preserved elderly man, with moderate cyanosis of the lips and nail beds. The temperature was 100° F., the pulse rate, 90, and the respiratory rate, 36. The fundi appeared normal except for arteriosclerotic changes. The lungs were resonant and no râles were audible. Examination of the heart revealed the apex impulse in the fifth intercostal space at the left anterior axillary line, a short, blowing, apical systolic murmur, normal rhythm, and sounds of poor quality. The blood pressure was 115/70. The edge of the liver was palpable beneath the right costal margin on deep inspiration; it was not tender. The reflexes were normal.

Urinalyses showed good concentration. One specimen showed a slight trace of albumin. All examinations of the urinary sediment were essentially negative. On admission the erythrocyte count was 5,000,000; the hemoglobin, 105 per cent (Sahli); and the leucocyte count, 12,800; a differential leucocyte count revealed 79 per cent polymorphonuclears, 21 per cent lymphocytes, 8 per cent monocytes, and 2 per cent eosinophiles. Three stools were negative for occult blood. The blood Hinton and Kahn reactions were negative. The icterus index was 6. The nonprotein nitrogen content of the blood was 31 mg. per cent. A roentgenogram of the chest, taken soon after entry, showed no parenchymal pulmonary lesion. Electrocardiograms showed left axis deviation, with intraventricular block and a deep S_2, but no definite changes indicative of recent infarction.

Because of the appearance of numerous ventricular premature beats shortly after the patient was admitted, 12 grains of quinidine sulfate were administered daily in four doses. On the fifth hospital day the dose was reduced to nine grains in twenty-four hours. The drug was omitted on the fifteenth day because of tinnitus in the left ear; this subsided within twenty-four hours. The temperature chart from the sixteenth hospital day to the time of discharge is reproduced herewith (Fig. 1),

Received for publication March 11, 1941.

and reference to it will facilitate an understanding of the subsequent course. Prior to this he was entirely afebrile. On the seventeenth hospital day the administration of the drug was resumed in a dosage of twelve grains a day. Two days later the temperature rose abruptly to 102.2°, and this fever was associated with chilliness and a mild injection of the throat. The fever persisted for three days, through the twenty-first hospital day. The throat cleared up within twenty-four hours.

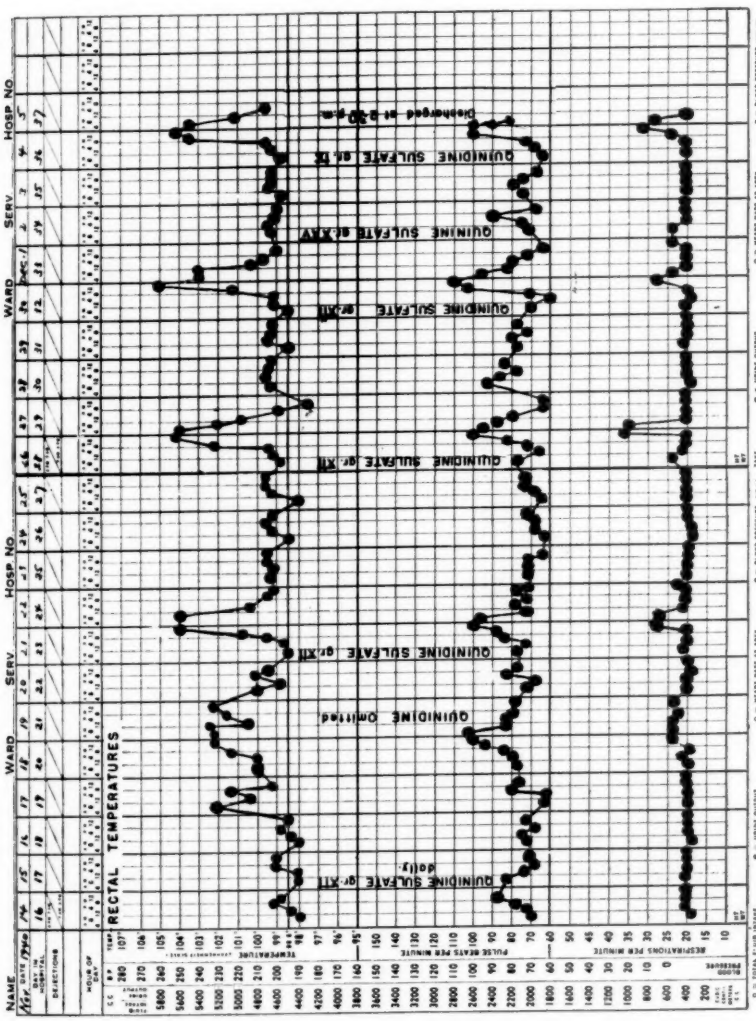

Fig. 1.

During this time the patient was receiving quinidine sulfate, theobromine-sodium-acetate, and chloral hydrate. On the twenty-first hospital day quinidine was discontinued and the temperature fell abruptly to normal. On the twenty-third hospital day quinidine therapy was resumed in the same dosage, and the temperature rose rapidly, reaching 104° by eight o'clock that evening. The leucocyte count decreased to 4,600 per cu. mm., and the tip of the spleen became palpable. The drug was again omitted on the same night, and all other medication was discontinued. The temperature immediately subsided, and he remained afebrile for the following three

days. At this point it seemed likely that we were dealing with a drug fever. To confirm this suspicion quinidine was again administered on the twenty-eighth hospital day, and all other medication was withheld. As on previous occasions, he was given three grains of the drug at eight A.M., noon, four P.M., and eight P.M. The temperature reached 104° that evening; the drug was discontinued, and the patient became afebrile by four P.M. on the following day. As Fig. 1 shows, this observation was repeated on two more occasions, on one of which the temperature rose to 105°. The leucopenia and splenomegaly did not recur. On each occasion the rise in temperature was accompanied by a corresponding increase in the pulse and respiratory rates. The patient had no other evidences of drug intoxication. He appeared quite well, even during the height of the fever, and complained only of feeling warm. The tinnitus never recurred. Plasma hemoglobin and bilirubin estimations were made before and during the administration of quinidine. There was essentially no change in the plasma hemoglobin, but a slight rise in bilirubin from 0.3 mg. per cent to 0.9 mg. per cent was demonstrated. The plasma hemoglobin was 3.2 mg. per cent before quinidine and 3.6 mg. per cent during its administration.

It is of interest that no febrile reaction resulted from the administration of quinine. The patient was given a total of 25 grains without any effect on the temperature.

SUMMARY

A marked rise in temperature, without other signs of toxicity, occurred repeatedly after the administration of quinidine in doses which are commonly employed therapeutically.

THIRTY YEARS AFTER LIGATION OF THE ANTERIOR DESCENDING BRANCH OF THE LEFT CORONARY ARTERY

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ON APRIL 18, 1909, a woman was admitted to the Pennsylvania Hospital shortly after having been stabbed in the left breast.

A diagnosis of wound of the heart was made, and the operative note, after describing opening the thorax and pericardium, informs us that "the heart was beating regularly and a gush of blood was coming with each systole from a cut about one inch long. A suture of linen thread was passed through the heart muscle, closing this (cut) partially. The blood from the upper end of the wound was bright, and from the lower end, dark. The wound was seen to cross a coronary vessel, and was apparently in the middle of the right ventricle. Five or six linen sutures closed the wound completely."

Actually, the wound crossed the anterior portion of the interventricular groove diagonally from the left above to the right below, about midway between the apex and the auriculoventricular groove, severing the descending branch of the left coronary artery. The patient was in the hospital from mid-April to mid-July, during which time she developed acute pericarditis, empyema, and lobar pneumonia; she was finally discharged "well and strong."

This patient reported to the Pennsylvania Hospital outpatient department October 24, 1940. She is a grandmother, and lives with the daughter, now married, whom she was nursing at the time of the accident. She takes her part in the daily housekeeping activities, climbs the stairs with impunity, and is as well and active as a 75-year-old woman could be expected to be; she presents no subjective symptoms of heart disease.

Examination showed that her blood pressure was 170/85; the pulse rate was 80, the pulse was regular in rhythm but not in force, and the arteries were not particularly sclerotic. The left breast was smaller than the right, and the scar, at the inner margin of the breast, was scarcely noticeable. The cardiac apex was in the fifth intercostal space, 8 cm. to the left of the midline; it was not diffuse and no thrill was felt. The right border of the heart was not displaced. A systolic murmur was heard all over the heart, perhaps best at the base. Expansion of the bases of the lungs was unequal; it was better on the right, where there were râles. There was a drainage scar in the axilla. There was no edema of the ankles or over the sacrum.

Received for publication March 18, 1941.

A roentgenogram of the thorax, made Feb. 13, 1940, was interpreted as follows: "The heart is not enlarged; there is good pulsation, and no limitation of motion due to the previous operative intervention. The arch of the aorta shows marked calcification. There is calcification of the pleura on the left side. The left half of the diaphragm is slightly elevated, but the diaphragm moves freely and equally on respiration."

An orthodiagram, made April 4, 1940, showed that the transverse diameter of the heart was 11 cm., with a thoracic diameter of 20.2 cm. Also, the heart was described as showing "very slight enlargement, both of the left ventricle and of the right outflow tract."

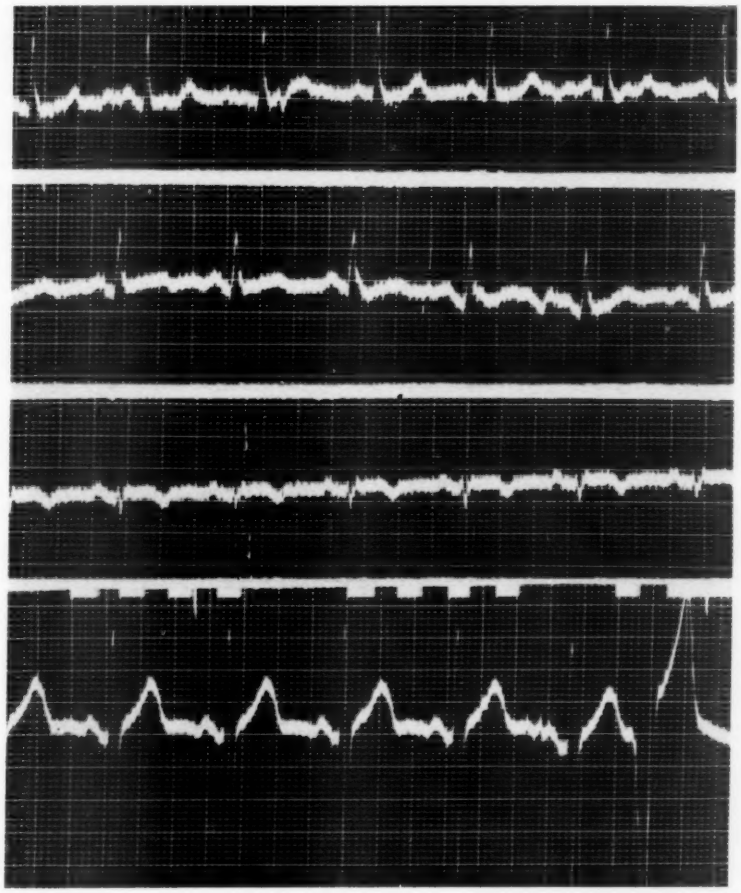

Fig. 1.

The electrocardiogram (Fig. 1) showed an occasional premature beat, a rate of 88, a P-R interval of 0.14 sec., no axis deviation, inversion of T_3, and low voltage of QRS in Lead III. The chest lead was normal. Such a curve is not abnormal for a person of this age, and is not diagnostic of heart disease.

This case was reported in 1913 (J. A. M. A., Nov. 15, 1913), four years after the accident. At that time attention was directed to the previously reported cases of wound of the heart, with severed coronary arteries. Three of the patients died soon after operation. Three (the present patient made four) had recovered from their operations; one patient (F. T. Stewart's first case) died of pulmonary tuberculosis and came to autopsy five years after operation.

The present patient is living and comfortable, 32 years after severance and ligation of the descending branch of her left coronary artery. As nearly as we can ascertain, she has no evidence of coronary disease, and she cannot be said to have any cardiac dysfunction.

Abstracts and Reviews

Selected Abstracts

The Abstracts in this number have been selected from the *Journal of the Mount Sinai Hospital*, New York, **8**: 1942, pages 321 to 1176, dedicated to Dr. Bernard S. Oppenheimer on the occasion of his sixty-fifth birthday.

Abramson, D. I.: Resting Blood Flow and Peripheral Vascular Responses in Different Portions of the Extremities, J. Mt. Sinai Hosp., New York, **8**: 328, 1942.

Certain conclusions can be drawn from the foregoing observations. First of all, since the hand contains arteriovenous shunts which evidently are under the marked control of the vasomotor center, the vascular responses in this region cannot be considered as representative of peripheral blood flow generally. Further, in contrast to the vascular responses in the hand, the blood flow to the normally innervated forearm and leg is more constant, not being diminished, at least, by most noxious stimuli. The arterioles in both types of vascular beds actively dilate for the purpose of heat dissipation, but differ in that those of the hand function under ordinary conditions, while those of the forearm and leg are affected only when the need is excessive. The vascular beds in the forearm and leg, therefore, are more satisfactory than the hand for studying the local effect of sudden changes in the systemic circulation. Finally, they are probably more truly representative of peripheral blood flow as it relates to the metabolic needs of the extremities.

AUTHOR.

Averbuck, S. H.: Acute Generalized Postoperative Peritonitis Simulating Coronary Artery Occlusion. p. 335.

The clinical picture of acute coronary artery occlusion may be simulated by many other supra- and infradiaphragmatic syndromes. There is a general awareness of this problem in differential diagnosis. Further emphasis, however, is required in connection with postoperative shock states which are too uncritically ascribed to acute coronary artery occlusion. Two cases of a rapidly spreading postoperative peritonitis accompanied by peripheral collapse and the clinical picture of shock are described. A diagnosis of acute coronary occlusion was made in each instance. Autopsy failed to disclose such a condition in either case. The clinical peculiarities of postoperative coronary thrombosis are commented upon and it is urged that definite confirmatory evidence be sought before making this diagnosis postoperatively in shock states. The value of the preoperative electrocardiogram as a basis of comparison for postoperative records is stressed.

AUTHOR.

Barnes, A. R., and Burchell, H. B.: The Significance of Negative T Waves in All Three Standard Leads of the Electrocardiogram. p. 346.

A study of T-wave negativity in all three leads of the electrocardiogram shows that this abnormality may occur in many conditions. T-wave negativity in all three

standard leads associated with upright QRS complexes is an occasional electrocardiographic pattern of strain of the left ventricle. T-wave negativity in all three standard leads may be an electrocardiographic pattern following acute coronary occlusion and if it is associated with a Q pattern the latter probably will be of the Q_3 type. The behavior of the T wave in the chest leads is not predictable when all three standard leads have negative T waves. A number of cases have been encountered with the electrocardiographic abnormality of negative T waves in all three leads, and in which the heart has been believed to be structurally normal.

AUTHORS.

Benjamin, J. E., Landt, H., and Landen, M.: Coronary Disease, Observations on Dispensary Patients. p. 376.

Thirty-six (18 per cent) cases coming to necropsy (1931 to 1941) were found to have myocardial infarction and coronary occlusion. Only four (11 per cent) patients had ever had actual attacks of "cardiac pain." Dyspnea, congestive failure and elevated arterial blood pressure were the outstanding symptoms. The importance of recognizing the picture of coronary obstruction with infarction, as associated with congestive failure only, and not necessarily pain, is stressed.

AUTHORS.

Boas, E. P., and Levy, H.: Angina Pectoris and the Peptic Ulcer Syndrome: Preliminary Report. p. 422.

The authors have presented cases to illustrate the intimate relationship that may be manifested between the symptoms of angina pectoris and those of peptic ulcer. There may be a sudden simultaneous onset of ulcer symptoms and of anginal symptoms. Repeated attacks of angina pectoris at rest ending in coronary thrombosis may occur two to three hours after meals and during the night at the characteristic "ulcer hours." When symptoms of angina pectoris and peptic ulcer co-exist, successful treatment of the ulcer symptoms may cause remission of the anginal syndrome. Epigastric localization of anginal pain may be conditioned by a pre-existing ulcer.

AUTHORS.

Conner, L. A.: The Heart in Fat Embolism. p. 454.

It is evident that in many if not most cases of fat embolism sufficiently severe to be of clinical significance the heart is involved in the embolic process and may play a part in the fatal issue when this occurs. It is doubtful, however, if such heart involvement ever gives rise to symptoms which are sufficiently characteristic to make the clinical diagnosis possible. The large literature on the subject contains no instances of fat embolism which have presented the classical picture of acute coronary occlusion, nor have postmortem studies ever disclosed an authentic example of myocardial infarction as the result of such embolism.

It is conceivable of course that some fragment of fatty tissue larger than the fat droplets might reach the left side of the heart through a patent foramen ovale (paradoxical embolus) and so result in coronary embolism, but no such happening is recorded and such a possibility is too remote to deserve clinical consideration.

The answer, then, to the question posed in the beginning is that there is no support for the view that fat embolism may at times present the clinical picture of coronary occlusion.

AUTHOR.

Crawford, J. H.: The Diagnosis of Aneurysm of the Heart. p. 469.

The signs which are most frequently present and appear to be most important in the diagnosis of aneurysm of the heart are: (a) A history of electrocardiographic proof of previous coronary occlusion. (b) The presence of an abnormal precordial pulsation distinctly separated from the apex pulsation particularly when it is situated above the fifth rib. (c) On x-ray examination a localized bulge which cannot be separated from the heart shadow in any view in which it can be seen or an angulation of the left border of the heart. (d) Systolic expansion in the region of the abnormality as seen on fluoroscopy or roentgenkymography is practically conclusive evidence and small or absent contractions in this area are strongly suggestive. (e) Localized pericardial adhesions or calcification of the aneurysmal wall or its contents are also of value when present.

The following conditions simulate aneurysm of the heart closely and must be carefully differentiated from it: (a) Tumor of the heart. (b) Aneurysm of a sinus of Valsalva. (c) Aneurysm of a coronary artery. (d) Calcification of the pericardium. (e) Diverticulum of the pericardium. (f) Loculated pericardial effusion. (g) Cyst of the pericardium.

AUTHOR.

Friedman, B., Jarman, J., and Marrus, J.: Therapeutic Agents and Renal Implantations in Experimental Hypertension. p. 534.

Studies of the blood pressure reducing properties of a number of "hypotensive" agents and of tissue implantations in rats with chronic hypertension of renal origin indicate as follows: Erythrol tetranitrate, bismuth subnitrate, allium sativum (garlic extract) and dried kidney tissue (nephritin) are without effect. Potassium thiocyanate in doses which, in proportion to body weight, are about 50 times those advocated for man, produce a slight decline in pressure accompanied by evidences of toxicity. Magnesium carbonate and sulphate are ineffective. An extract of kidney (Page) reduced blood pressure to the normal level during the period of administration of the extract. A fall in blood pressure occurs following subcutaneous implantation of strips of tissue taken from the kidney, liver and spleen. The depressor effect is correlated with the presence of localized necrotic tissue and does not seem to be specific for the kidney.

AUTHORS.

Globus, J. H., and Schwab, J. M.: Intracranial Aneurysms: Their Origin and Clinical Behavior in a Series of Verified Cases. p. 547.

A review of the clinical and anatomical features in thirteen cases of intracranial aneurysms led to the following observations: Intracranial aneurysms pre-exist a terminal fatal event by varying lengths of time, in some instances by as many as thirty years and probably longer. In the great majority of instances the life history of an aneurysm is punctuated by two or more explosions characterized commonly by manifestations of subarachnoid bleeding. A fatal issue usually results from the rupture of the aneurysm and extravasation into an area of previously disintegrated brain tissue, ultimately leading to intraventricular hemorrhage. In a few instances death is caused by the effect of the pressure expansion of the aneurysm without its rupture and without tissue disintegration.

Disintegration of brain tissue and hemorrhage into the areas of softening with extension into the ventricles is most commonly encountered in an aneurysm arising from the rostral part of the circle of Willis (anterior communicating, anterior cerebral and internal carotid arteries), while aneurysms of the posterior part of the circles (posterior cerebral, basilar and vertebral), exhibit manifestations of an ex-

panding lesion. Generalized cerebral arteriosclerosis was not common with the aneurysms in this series, there being advanced atheromatous changes in cerebral vessels of two cases, moderate changes in four and none at all in seven instances of our series. This would point, as far as this material is concerned, to the significance of the congenital origin of aneurysms. Syphilitic and mycotic aneurysms were not among this series, indirectly indicating their rarity. The aneurysms were single in all but one case, in which they were multiple. Hypertension was not a frequent accompanying condition, as it was found in only three of the thirteen cases.

The age distribution shows that fatal manifestations of an existing aneurysm usually appear during the third and fourth decades of life, but there is evidence that their silent existence precedes the fatal issue by many years. Aneurysms seem to be evenly distributed between the two sexes.

Clinically the aneurysms occasionally simulate the picture of brain tumor, encephalitis or vascular disorder of a less defined type; signs of increased intracranial tension, however, except headache, were found in few instances, and mainly when the aneurysm was more caudal in location; papilledema was rare; focal signs (often) of localizing character were frequent. Convulsive seizures occurred and, in some instances, had a focalizing value, but when they were concomitant with bleeding into the subarachnoid space, they had no localizing significance. Signs of meningeal irritation when present were indicative of subarachnoid bleeding. The cerebrospinal fluid was often bloody or xanthochromic, indicating recent or older bleeding. Occasionally a high leucocyte count was encountered in the cerebrospinal fluid, leading to the erroneous diagnosis of a septic meningitis. The blood occasionally revealed a leucocytosis, usually found in the course of an episode of subarachnoid bleeding.

AUTHORS.

Goldblatt, H., Braden, S., Kahn, J. R., and Hoyt, W. A.: Studies on Experimental Hypertension. XVI. The Effect of Hypophysectomy on Experimental Renal Hypertension. p. 579.

In agreement with Page and Sweet it has been shown that complete hypophysectomy does not prevent the development of experimental renal hypertension and that it tends to lower slightly the blood pressure of normal animals. In the hypophysectomized animals that did not develop renal excretory insufficiency (the benign phase) the hypertension persisted at high levels for a long time. The malignant phase of this type of hypertension was also observed in an animal that had been completely hypophysectomized. This rules out the hormones of the pituitary body as playing a significant part in the pathogenesis of the arteriolar lesions observed in the organs of animals in the malignant phase of hypertension.

The effect of any surgical procedure, including hypophysectomy, on established experimental renal hypertension must always be evaluated with caution because in some hypertensive animals, even without any type of treatment, there is a tendency for the blood pressure to reach lower levels. It is considered, therefore, that more significance should be attached to the finding that experimental renal hypertension cannot be prevented by hypophysectomy than to the effect of this procedure on previously hypertensive animals.

The results of this study lend no support to the view that the hypophysis plays a significant part in the pathogenesis of experimental hypertension due to constriction of the main renal arteries or of any similar type of human hypertension and offers no justification for surgical or other interference with the integrity of the pituitary body for the treatment of any type of human hypertension that resembles experimental hypertension of renal origin.

AUTHORS.

Harkavy, J.: Vascular Allergy. II Manifestations of Polyvalent Sensitization. p. 592.

Four cases presenting cardiovascular involvement in which capillaries, veins and arteries participated, are reported. Constitutional allergy or atopy was present in three of the four patients. The exciting agents proved to be drugs, tobacco, pollen, foods and bacteria. The various manifestations are regarded as the expression of vascular allergy.

AUTHOR.

Harrison, T. R.: Clinical Syndromes Produced by Temporary Disturbances of the Cerebral Circulation. p. 612.

The foregoing discussion is admittedly incomplete. The author's object has been to consider a group of allied disorders from an illustrative rather than from a comprehensive standpoint. A more complete exposition would have to include other disorders, such as acute mountain sickness, for example. It is probable that in the future new clinical syndromes which fall into the general group of temporary disturbances of the balance between the oxygen supply and the oxygen need of the brain will be described. In any case it would seem that supplementing the usual etiologic and pathologic points of view by attempting a physiologic approach will be helpful in understanding this complex but common and important group of conditions.

AUTHOR.

Hitzig, W. M.: On Mechanisms of Inspiratory Filling of the Cervical Veins and Pulsus Paradoxus in Venous Hypertension. p. 625.

Inspiratory filling of the cervical veins is a nonspecific phenomenon; it occurs not only in chronic constrictive pericarditis, but also in syndromes of venous hypertension (without mediastinitis) such as severe right heart failure (combined type) and superior vena caval obstruction. It is of diagnostic significance in chronic constrictive pericarditis only when it is accompanied by a pulsus paradoxus. The "paradoxical" phenomenon of inspiratory filling of the cervical veins can be demonstrated manometrically by measuring the venous pressure in the veins of the neck. The elevation of the cervical venous pressure in the syndromes studied ranged from ½ to 3½ cm.

Manometric observations reveal that inspiratory filling of the neck veins occurs much more frequently than is clinically suspected. This is due to the fact that preexisting elevation of the venous pressure interferes with the clinical evaluation of increased distention of the cervical veins during inspiration.

Inspiratory filling of the cervical veins in heart failure represents an imbalance between an abnormally augmented venous return from the abdomen and a diminished right ventricular output. The central venous stasis which surrounds an overloaded right heart retards the venous return from the upper part of the body. This is promptly reflected into tributaries of the superior vena cava, where it causes either visible filling of the veins or manometric elevation of the venous pressure. Inspiratory filling of the cervical veins in superior vena caval obstruction occurs when the circulatory dynamics indicate that the closure is below the azygos vein. In these cases, the inspiratory descent of the diaphragm compresses the inferior vena cava and retards the blood flow through the collateral circulation and the intraabdominal veins.

Paradoxical elevation of the cerebrospinal fluid pressure paralleling the inspiratory rise of the antecubital venous pressure was observed in one case of superior vena caval obstruction. It is suggested that a similar cerebrospinal fluid phenomenon will appear in those "congestive" states which manifest inspiratory filling of the cervical veins (clinically or manometrically).

A concept is proposed in explanation of the genesis of pulsus paradoxus in pericardial effusion. The phenomenon, which may be regarded as a functional exaggeration of normal cardiorespiratory dynamics, will appear when there is a marked discrepancy between the pulmonary blood volume during expiration and the pulmonary vascular capacity during inspiration. This concept can be similarly applied to constrictive pericarditis when the compression is predominantly right-sided and to the "dynamic" forms of pulsus paradoxus associated with laryngeal and intrathoracic tumors.

The mechanical concept of the cause of inspiratory filling of the cervical veins and pulsus paradoxus cannot be ignored in some cases of constrictive pericarditis, but its occurrence in syndromes of venous hypertension (without mediastinitis) favors the cardiorespiratory or dynamic concept.

A "paradoxical pulse" that appears only in certain positions of the arm occurs as a result of abnormal anatomical relations between the subclavian artery and the first rib and the clavicle. The inspiratory weakening of the pulse is localized to the involved extremity in contrast to the generalized "pulsus paradoxus" of cardiopulmonary origin.

AUTHOR.

Krumbhaar, E. B.: A Congenital Cardiac Anomaly: Atresia of Mitral Orifice and Separation of Left Auricle and Ventricle. With an Appended Case of Absent Left Ventricle. p. 737.

A heart of a stillborn infant is reported, in which the left auriculoventricular orifice was obliterated, and the left auricle separated from the left ventricle by a distance of several millimeters. From the diminutive left ventricle, which was connected with the large right ventricle by a small septal defect, a small aorta (?) emerged that communicated with the large pulmonary artery (?) by a widely patent ductus arteriosus. The foramen ovale was widely open. The coronary arteries arose from the large artery. Other congenital anomalies were present, the unilateral ones all being on the left side. The heartbeat was heard before and after delivery, but the child did not breathe or move.

AUTHOR.

Levine, S. A., and Kauvar, A. J.: The Association of Angina Pectoris or Coronary Thrombosis With Mitral Stenosis. p. 754.

A study was made of 38 cases having both mitral stenosis and angina pectoris, 16 of which were examined post mortem. It was found that 17 of 2832 cases of coronary artery disease seen in private practice had mitral stenosis, i.e., 0.6 per cent. These 17 cases of mitral stenosis with angina or coronary thrombosis were observed among 741 consecutive cases of mitral stenosis, i.e., 2.6 per cent.

The incidence of significant coronary artery disease among 314 cases of mitral stenosis examined post mortem was 5 per cent. The average age for the onset of angina was 50.4 years for women and 53.7 for men, the duration of angina being about 4 years in both sexes. Whereas in ordinary cases of angina men predominate about 3 to 1 and die at a younger age, in these cases of angina and mitral stenosis women predominate 2 to 1 and die at a younger age.

Among the 16 cases examined post mortem, the average blood pressure of the women was 175 systolic and 93 diastolic, and for the men 146 systolic and 88 diastolic. The blood pressure for the other cases was somewhat lower.

Seventeen cases had permanent auricular fibrillation. In 5 of the 11 that had congestive failure, angina developed after the initial symptom of dyspnea. Three of the 16 cases examined post mortem showed no significant pathological changes in the coronary arteries. The finding of normal coronary arteries in these 3 cases and

in 9 similar cases reported by other observers indicates that in mitral stenosis factors other than coronary sclerosis may be responsible for the occurrence of angina pectoris. In the great majority of instances, however, when mitral stenosis and angina coexist, the two conditions are independent of each other, the former due to rheumatic infection and the latter the result of ordinary artery sclerosis.

AUTHORS.

Longcope, W. T., Fisher, A. M.: Involvement of the Heart in Sarcoidosis or Besnier-Boeck-Schaumann's Disease. p. 784.

In a series of 31 cases of sarcoidosis six patients showed some evidence of myocardial insufficiency during life or sarcoids of the heart and pericardium were discovered at autopsy. In one patient who showed no abnormalities of the heart during life a few lesions were found scattered through the myocardium at autopsy. The remaining five patients presented some evidence of disease of the heart. Three of the patients died. Autopsies performed on two of these cases showed sarcoidosis of the myocardium and pericardium.

The five patients suffered from various degrees of heart failure, often with enlargement of the heart, arrhythmias and electrocardiographic changes.

AUTHORS.

Mann, H., and Mayer, M. D.: The Uterine Electrocardiogram. p. 805.

A series of electrocardiograms were taken of a fetus in utero 6 days before a Caesarean operation, of the fetus in utero during the operation, after the uterus had been exposed and of the infant at intervals after birth. Electrodes placed directly on the exposed uterus gave a clear fetal curve without any perceptible maternal deflections. General anesthesia and the operative procedure produced no obvious change in the rate or rhythm of the fetal heart. Changes in the infant's electrocardiogram during the first few weeks are recorded in serial electrocardiograms.

AUTHORS.

Prinzmetal, M., Kayland, S., Margoles, C., and Tragerman, L. J.: A Quantitative Method for Determining Collateral Coronary Circulation: Preliminary Report on Normal Human Hearts. p. 933.

A quantitative method for determining the percentage of collateral circulation between the right and left coronary arteries is presented.

This procedure was performed on 12 normal hearts from patients ranging in age from three to sixty-seven years. Collateral circulation was found in all but one; the range being from 0 to 8.6 per cent. The average value obtained was 4.16 per cent. The average flow from the left to the right coronary artery was 19.2 c.c., or 4.55 per cent, of the flow through the left coronary artery, while the average collateral flow from the right to the left coronary artery was 6.2 c.c., or 4.05 per cent, of the flow through the right coronary artery.

The collateral circulation which has been demonstrated between normal coronary arteries, is ready to function immediately when the need arises. If a radiopaque substance, having a viscosity approximately that of blood, is injected into either coronary artery of a normal heart, the entire coronary artery bed is filled, further proving the presence of collateral circulation. If this same radiopaque substance is injected into the anterior descending or the circumflex branch of the left coronary artery of normal hearts, the entire coronary artery tree is filled. It has been shown that collateral vessels are sufficiently wide to permit passage of erythrocytes. This proves the physiologic usefulness of the collateral vessels.

The efficacy of the collateral circulation between the coronary arteries and its branches probably depends not only on the magnitude of the collateral, but also on such other factors as the size of the occluded vessel and the metabolic needs of the ischemic muscle.

AUTHORS.

Robb, J. S., Dooley, M. S., and Robb, R. C.: Displacement of the RS-T Segment by Potassium Chloride. p. 946.

Application of potassium chloride to the surface of the mammalian ventricle does not necessarily cause a greater RS-T displacement than does deep injection.

No support is obtained for the theory that the electrocardiogram is merely the summation of a dextro- and a laevo-cardiogram.

When leads I and III show RS-T deviation in opposite directions the lesion is not necessarily near the septum nor is the lesion necessarily anterior or posterior. When all three standard leads show an RS-T deviation in one direction the lesion is not necessarily limited to one ventricle.

It is again shown that where "injury" is limited to a single ventricular muscle band, a characteristic electrocardiogram results. "Injury" may be of various types, chilling, mechanical blows, pinching, ischemia, undue stretching, or the application of potassium chloride, in fact any agent resulting in the depolarization of a membrane. We have shown that regardless of the type of noxious agent, the result of injury localized to one muscle alone is constant in its effect on RS-T shifts in the electrocardiogram.

AUTHORS.

Schwartz, S. P.: Transient Ventricular Fibrillation: A Study of the Fibrillary Process and Its Development in Man. p. 1005.

An electrocardiographic study was made of the fibrillary process and its mode of development in eight patients who experienced such seizures. These records were compared with those obtained from animals (frogs, rats, dogs, cats and sheep) following faradization of the ventricles, poisoning with drugs or after ligation of the coronary arteries.

The preliminary alterations in the rhythm of the heart that lead to transient ventricular fibrillation consist of (a) an acceleration of the basic ventricular rate during the presence of some form of auriculoventricular dissociation; (b) the onset of "initial" premature beats arising from a constant focus in the ventricles as judged by their persistent similarity; and, (c) the development of short runs of irregular ventricular oscillations which increase progressively in duration and recur from moment to moment.

It appears that these short recurring periods of ventricular irregularities are the "initial" fibrillary periods of the ventricles. They are a distinct and unique feature in man and have not been noted in animals. They invariably foreshadow the appearance of longer seizures. The "initial" premature beats of the ventricles are associated clinically with an effective ventricular contraction which is audible at the apical region of the heart. The "initial" fibrillary periods are associated clinically with progressively diminishing heart sounds for the first 2 or 3 oscillations. The heart sounds disappear entirely after the fourth oscillation and because of the diminished blood supply to the brain, consciousness is lost if they last 20 to 40 seconds. A typical Adams-Stokes seizure with epileptiform convulsions, apnea and incontinence of feces and of urine supervenes if these oscillations last longer than 40 seconds.

The ventricular oscillations that yield these Adam-Stokes seizures are of two distinct types. One type of deflection is uniform in character, rising and falling

evenly to a base line with an amplitude of 8 to 10 mm. and a frequency of 130 to 300 oscillations per mnute.

With progressive asphyxia of the heart, the rate may be lowered to 90 per minute. The QRS complexes are continuous with each other so that the T waves are totally absent. This mechanism may be considered as one of ventricular flutter.

The second type consists of irregular oscillations averaging 130 to 460 per minute and varying in amplitude from 3 to 18 mm. in height. They differ in shape, size and form as well as frequency, duration and amplitude from record to record and moment to moment. Periodic waxing and waning of the height of the oscillations may be present and occasionally alternation of the ventricular complexes may be seen. They may persist as long as 6 minutes at one time and as many as 300 periods have been recorded in one patient during 24 hours.

Transient ventricular flutter and fibrillation may be ended by a single premature beat of the ventricles, a succession of these, or a run of ventricular tachycardia. A postundulatory pause, however, invariably precedes recovery.

The auricles maintain their regular rate and rhythm during ventricular fibrillation except in the longer periods when they may be slowed with an irregular rate and at times stand still because of asphyxia.

Except for the frequency and duration and its unusual transient, recurrent and reversible nature associated with profound clinical disturbances, the fibrillary process in man is identical with that in animals.

AUTHOR.

Sprague, H. B.: Syphilitic Aortitis With Aortic Regurgitation: An Electrocardiographic and Autopsy Survey at the Massachusetts General Hospital. p. 1034.

A series of 22 cases of syphilitic aortitis with aortic regurgitation autopsied at the Massachusetts General Hospital from 1926 to 1941 has been analyzed with reference to the electrocardiographic findings. The absence of left axis deviation in the electrocardiogram suggests a complication beyond simple aortic dilatation with involvement of aortic cusps and separation of their commissures. Conditions resulting in acute, or chronically mild strain on the left ventricle, or conditions resulting in an additional strain on the right ventricle appear to be largely responsible for the appearance of a normal electrical axis or a right axis deviation. In cases with bundle branch block, high degrees of coronary obstruction may be present, particularly of the right coronary orifice. But in one case without coronary narrowing, a large aneurysm pressing on and finally perforating into the pulmonary artery was found at autopsy. It is suggested that the electrical axis of the electrocardiogram is of more use than the S-T and T segments in indicating complications of syphilitic aortitis.

The results of this study afford another example of the fact that the extent of disease and the presence of complications are often of more importance than an etiologic factor alone in the production of alterations in the electrocardiogram.

AUTHOR.

Steele, J. M.: Comparison of Simultaneous Indirect (Auscultatory) and Direct (Intra-Arterial) Measurements of Arterial Pressure in Man. p. 1042.

Concerning the comparison of simultaneous measurements of arterial pressure obtained by direct intra-arterial manometry and by indirect auscultatory technique in 39 individuals, it may be said that:

Systolic pressure was underestimated in indirect measurement by about 10 mm. Hg. In the present study, the indirect pressure in the brachial was compared with the direct pressure in the radial artery. This procedure may account for half of this difference.

In auscultatory technique the disappearance of sound proved to be a more accurate measure of diastolic pressure than the sudden muffling. The former overestimated diastolic pressure by 8.8 mm. Hg, the latter by less than one.

The indirect auscultatory method of estimating arterial pressure is, considering its convenience and simplicity, an unusually accurate bedside method.

AUTHOR.

Sussman, M. L., and Dack, S.: The Roentgenkymogram in Myocardial Infarction. III. Cases With Normal Electrocardiogram. p. 1064.

A detailed analysis is presented of 18 cases of coronary occlusion in which the electrocardiogram returned to normal but abnormal ventricular contraction, demonstrated roentgenkymographically, persisted. This indicates the importance of the latter examination in cases in which symptoms of coronary disease or occlusion are present but other objective confirmation is lacking.

AUTHORS.

Wechsler, I. S., and Bender, M. B.: The Neurological Manifestations of Periarteritis Nodosa. p. 1071.

Seven cases of periarteritis nodosa with neurological manifestations are described. The most characteristic nerve disorder in this disease is involvement of single or multiple peripheral nerves in the extremities. The nerves are usually affected individually and at different times. Signs of central nervous system involvement are also present but are never striking, chiefly because gross lesions of the brain or spinal cord in periarteritis nodosa are uncommon. Renal damage and associated arterial hypertension may explain some of the symptoms of brain involvement in periarteritis nodosa.

AUTHORS.

White, Paul D., and Blumgart, H. L.: Cessation of Repeated Pulmonary Infarction and of Congestive Failure After Termination of Auricular Fibrillation by Quinidine Therapy. p. 1095.

Dr. B. S. Oppenheimer, in 1922, in his paper on "Results with Quinidine in Heart Disease," described his experience with two patients who, during the course of auricular fibrillation, had hemiplegia due to emboli. Both subsequently responded to quinidine by a change to sinus rhythm without suffering from a recurrence of symptoms of embolism, either during or after the treatment.

In further development of this same theme, we have herewith reported two patients in whom the administration of quinidine with consequent return to normal rhythm was undertaken despite generally accepted contraindications. This was followed by abrupt and striking improvement, with cessation of pulmonary embolism in Case 1 and of congestive failure in Case 2. In Case 1 the improvement has persisted to the time of writing. In Case 2 quinidine was probably life-saving at the moment, the patient surviving nearly three years before eventual death from his circulatory disease.

AUTHORS.

Wilson, F. N.: Concerning the Form of the QRS Deflections of the Electrocardiogram in Bundle Branch Block. p. 1110.

Multiple unipolar precordial leads have been employed in a large series of cases in which bundle branch block was thought to be present. In the vast majority of instances the use of such leads made it possible to determine whether bundle branch

block was present, and if so, whether the conduction defect was in the right or in the left bundle branch.

A diagnosis of complete bundle branch block should not be based upon the limb leads alone when the QRS interval measures appreciably less than 0.12 second. When the QRS interval equals or exceeds this value, the presence of a conspicuous S deflection in Lead I indicates that the conduction defect is on the right side. The absence of such a deflection indicates that the conduction defect is on the left side.

The position of the heart has a profound influence upon the form of the QRS complex in limb leads. In bundle branch block, the human heart is usually in such a position that the potential variations of the left arm resemble those of the left ventricular surface while the potential variations of the left leg are either small or like those of the right ventricular surface. When the position of the heart is such that these relations are reversed, left branch block may be mistaken for right branch block and vice versa if precordial leads are not taken.

AUTHOR.

Wolferth, C. C.: Relationship Between Biliary Tract Disease and Heart Disease. p. 1121.

Available evidence appears to indicate that the co-existence of biliary tract disease and coronary disease is significantly greater than is to be expected from the incidence of the two diseases. The cause for this co-existence is not clear. There is no good reason at present for believing that coronary disease causes biliary tract disease. Likewise, there is no valid evidence to support the view that biliary tract disease causes coronary disease. It is possible that similar metabolic faults, infections, or errors in the regimen of life may be factors in the production of both conditions but this view, however reasonable, is not as yet supported by actual evidence.

Biliary tract disease and heart disease may under certain circumstances mimic one another. Passive congestion of the liver may be mistaken for gall bladder disease. The anginal syndrome may be simulated by spasm of the digestive tube. It is possible that reflexes from the heart may affect the digestive tract and that reflexes from the digestive tract may affect the heart. Acute coronary occlusion and acute upper abdominal emergencies may furnish difficult problems in differential diagnosis.

The therapy of biliary tract disease may require modification in the direction of conservatism because of co-existing heart disease. Although cardiac symptoms may be improved following surgery on the gall bladder, such improvement occurs in only a minority of cases. Furthermore heart disease adds to the risk of operation. Consequently the presence of heart disease should be looked upon more as a contra-indication to operation than as an indication for operation. When, however, biliary tract disease threatens life or causes distressing symptoms, which cannot be controlled by conservative treatment, it may become necessary to accept the risk of operation even in the presence of serious heart disease.

AUTHOR.

Wright, I. S.: Physical Measures in the Treatment of Peripheral Vascular Disease. p. 1128.

An effort has been made to evaluate the present usefulness of various physical measures in the treatment of peripheral vascular diseases. It should be pointed out that these agents represent only a portion of the whole therapeutic picture, which also includes the problems of tobacco, the local care of the lesions and of the extremities, the use of drugs, typhoid vaccine, tissue extracts, alcohol and the

numerous techniques in the surgical field. Anyone purporting to treat these conditions must be thoroughly familiar with the entire field of therapy.

Physical agents are, however, important and it appears well worth while to review their indications and contraindications at this time. Today many of these problems are controversial. The final answers must await the accumulation of further clinical experience and experimental data.

AUTHOR.

Yater, W. M.: Calcification of the Pericardium and Chronic Cardiac Compression: Report and Discussion of Four Cases. p. 1144.

Four cases of calcification of the pericardium have been reported, all showing definite evidence of chronic cardiac compression. It is a relatively rare lesion but is probably always associated with sufficient fibrosis and rigidity of the pericardium to handicap the heart in its function. Ascites is not the constant feature usually thought, and symptoms of circulatory embarrassment may be slight. Partial heart block occurred in two of the cases, auricular fibrillation in two, and right axis deviation in two. Operation is naturally more difficult than in the cases of cardiac compression without calcification. A probable tuberculous etiology existed in one case and a possible tuberculous etiology in two others. In the fourth, no etiologic agent was suggested.

AUTHOR.

Miscellaneous Abstracts

Schroeder, H. A., and Neumann, C.: Arterial Hypertension in Rats. II. Effects on the Kidneys. J. Exper. Med. **75**: 527, 1942.

When rats developed cardiac hypertrophy or elevation of blood pressure as a result of one of several methods designed to bring about arterial hypertension, renal vascular disease occurred frequently.

When injury to one kidney was followed by cardiac hypertrophy or elevation of blood pressure, vascular lesions were found with considerable regularity in the opposite one, as well as in the one injured.

Renal lesions rarely occurred in the absence of cardiac hypertrophy or elevated blood pressure.

Renal vascular lesions in rats are occasioned, therefore, by injury to one kidney and are usually associated with, and dependent on, the presence of arterial hypertension.

AUTHORS.

Marvin, H. M.: The Use and Abuse of the Electrocardiogram in Medical Practice. New England J. Med. **226**: 213, 1942.

One of the principal reasons the electrocardiographic method is doing widespread harm today is that many physicians overemphasize its value and underestimate its limitations. They confidently expect it to accomplish much the same things that a surgeon expects of an exploratory laparotomy: that it will disclose the nature of the pathologic process, reveal its exact location and extent, and tell a great deal about the immediate treatment and prognosis. They fail to realize that it is purely a laboratory procedure, comparable in many respects with a roentgenogram or a leucocyte count. As such, the electrocardiogram is to be interpreted merely as one finding among many, and in the light of all the clinical evidence and

other laboratory tests. With the exception of the arrhythmias and some cases of acute myocardial infarction, it is reprehensible to attempt an interpretation of the electrocardiogram without knowing the clinical findings and the clinical diagnosis.

AUTHOR.

Harris, A. S., and Moe, G. K.: Idioventricular Rhythms and Fibrillation Induced at the Anode or the Cathode by Direct Currents of Long Duration. Am. J. Physiol. 136: 318, 1942.

By use of the donor-tagged cell method for the determination of red cell volume in dogs, it has been shown that in the individual dog a linear relationship exists between the red cell volume and the jugular hematocrit over a hematocrit range of from 11 to 57 per cent.

It is suggested that the total plasma volume as determined by commonly employed methods is not necessarily representative of the actively circulating plasma volume.

AUTHORS.

Irvine, A. D.: Coarctation of the Aorta. Canad. M. A. J. 46: 436, 1942.

Coarctation of the aorta is one of the more rare anomalies of the cardiovascular system. Although present during infancy and childhood it usually does not become manifest till adolescence or early adult life.

The most important change occurring in the vascular system is the development of a collateral circulation between the proximal and distal aortic segments. This is chiefly by the scapular, mammary and intercostal arteries.

Clinically, the condition is diagnosed by the hypertension in the upper portions of the body contrasted with the hypotension in the lower, coupled with evidence of dilated collateral arteries.

Radiologically, the findings of smooth notching in the inferior surfaces of the ribs is pathognomonic. This so-called Rosler's sign is not present in all cases. It is due to the dilated tortuous intercostal arteries which take part in the collateral circulation.

Three cases of coarctation of the aorta discovered accidentally and confirmed by subsequent clinical examination are reported.

AUTHOR.

Book Review

A BIBLIOGRAPHY OF AVIATION MEDICINE: Compiled by Ebbe Curtis Hoff and John Farquhar Fulton, Charles C Thomas, Springfield, 1942, 237 pages, 6,029 entries, $4.00.

Perhaps it is axiomatic that, in ordinary times, nothing is more tedious or less appreciated than the labors of bibliographers and lexicographers, but the hard work that produced this excellent compilation will surely be rewarded, for the book is timely and comprehensive, and therefore indispensable to workers in its field. Important, also, is the compilers' thorough grasp of the fact that the subject is not new, but has its roots in the work of Boyle, Bert, Torricelli, and Pascal.

The arrangement and indices leave nothing to be desired.

HORACE M. KORNS.

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THE American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of twenty-seven eminent physicians who represent every portion of the country.

A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

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The Association earnestly solicits your support and suggestions for its work. Membership application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.

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